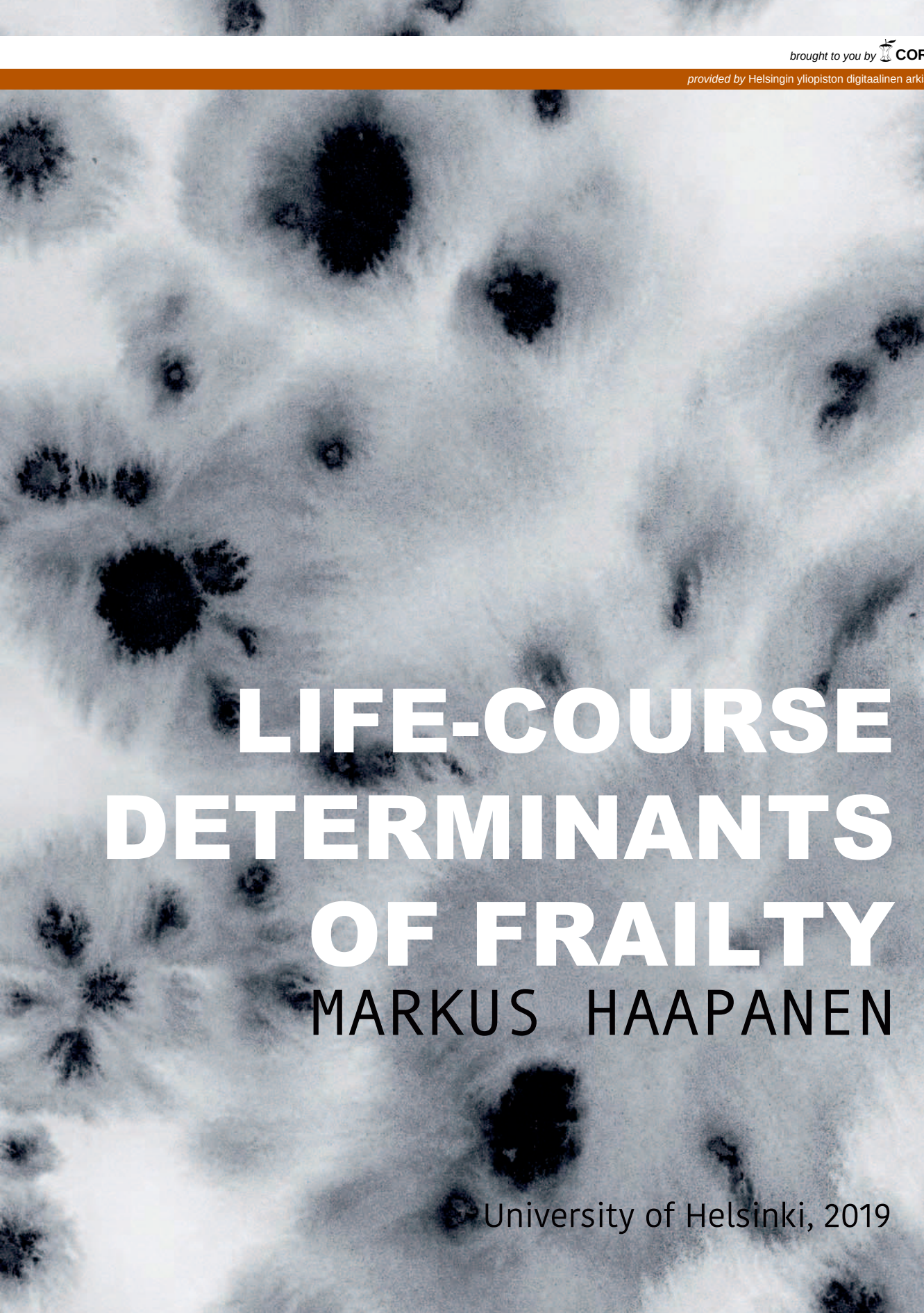

LIFE-COURSE DETERMINANTS OF FRAILTY

MARKUS HAAPANEN

University of Helsinki, 2019

Department of General Practice and Primary Health Care
University of Helsinki, Helsinki, Finland
and
Folkhälsan Research Centre, Helsinki, Finland

LIFE-COURSE DETERMINANTS OF FRAILTY

Markus Jaakko Olavi Haapanen

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of
the University of Helsinki, for public examination in Pieni juhlasali,
University Main Building, on May 31, 2019, at 12 noon.

Helsinki 2019

HELSINGIN YLIOPISTO

Cover design by Saana Pitkänen

ISBN 978-951-51-5149-0 (pbk.)
ISBN 978-951-51-5150-6 (PDF)

Hansaprint
Helsinki 2019

Supervised by

Professor Johan Eriksson, MD, DMSc
Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland and Folkhälsan Research Centre, Helsinki, Finland

Docent Mikaela von Bonsdorff, PhD
Faculty of Sport and Health Sciences and Gerontology Research Centre, University of Jyväskylä, Jyväskylä, Finland and Folkhälsan Research Centre, Helsinki, Finland

Reviewed by

Professor Riitta Antikainen, MD, DMSc
Centre for Life Course Health Research/Geriatrics, University of Oulu, Oulu, Finland and Medical Research Centre, Oulu University Hospital and University of Oulu, Oulu City Hospital, Oulu, Finland

Associate Professor Anna-Maija Tolppanen, PhD
School of Pharmacy, University of Eastern Finland, Kuopio, Finland

Opponent

Professor Emeritus Jaakko Valvanne, MD, DMSc
Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland and Gerontology Research Centre, University of Tampere, Tampere, Finland

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Haapanen MJ, Perälä M-M, Salonen MK, Kajantie E, Simonen M, Pohjolainen P, Eriksson JG, von Bonsdorff MB. Early life determinants of frailty in old age: the Helsinki Birth Cohort Study. Age and Ageing 2018; 47: 569-575.

II Haapanen MJ, Perälä M-M, Osmond C, Salonen MK, Kajantie E, Rantanen T, Simonen M, Pohjolainen P, Eriksson JG, von Bonsdorff MB. Infant and childhood growth and frailty in old age: the Helsinki Birth Cohort Study. Ageing Clin Exp Res 2018; [Epub ahead of print].

III Haapanen MJ, Perälä M-M, Salonen MK, Kajantie E, Simonen M, Pohjolainen P, Pesonen AK, Räikkönen K, Eriksson JG, von Bonsdorff MB. Early life stress and frailty in old age: the Helsinki Birth Cohort Study. BMC Geriatrics 2018; 18(1): 179.

IV Haapanen MJ, Perälä M-M, Salonen MK, Guzzardi MA, Iozzo P, Kajantie E, Rantanen T, Simonen M, Pohjolainen P, Eriksson JG, von Bonsdorff MB. Telomere length and Frailty: the Helsinki Birth Cohort Study. J Am Med Dir Assoc 2018; 19(8): 658-662.

The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

ADL	Activities of daily living
BDI	Beck Depression Inventory
BMC	Bone mineral content
BMI	Body mass index
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CV	Coefficient of variation
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
DOHaD	Developmental Origins of Health and Disease
ELS	Early life stress
HBCS	Helsinki Birth Cohort Study
HPA	Hypothalamus-Pituitary-Adrenal cortex
HUCH	Helsinki University Central Hospital
IADL	Instrumental activities of daily living
IGF	Insulin-like growth factor
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
IL	Interleukin
INF	Interferon
LTL	Leukocyte telomere length
LTPA	Leisure time physical activity
OR	Odds ratio
PCR	Polymerase chain reaction
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RRR	Relative risk ratio
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
TNF	Tumor necrosis factor
TRF	Terminal restriction fragments
WHO	World Health Organization
WWII	World War II

ABSTRACT

The proportion of those aged 60 years and older is expected to double from 12 to 24 per cent by the year 2050. The prevalence of frailty increases rapidly with older age and is characterized by loss in biological reserve and resistance to stressors across several physiological systems. Frail people are at an increased risk of adverse health outcomes including hospitalization and premature mortality. Effective prevention of frailty requires knowledge on its risk factors across the life course. The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that early life influences may be important in determining disease risk in adulthood. There is evidence of early life influences in the pathogenesis of chronic diseases including cardiovascular disease and type 2 diabetes. The aim of the present study was to investigate early life exposures and frailty from a life-course perspective.

The present study uses data from the Helsinki Birth Cohort Study that includes 8,760 individuals born in Helsinki in 1934-1944. A random subset of participants (n=2,902) was invited to participate in a baseline clinical examination; of those 2,003 participated in 2001-2004. Of these, 1,094 out of the invited 1,404 participated in a follow-up clinical examination in 2011-2013. Frailty was measured at the follow-up examination using the Fried phenotype model in participants with a mean age of 71 years. Data on infant and childhood development and exposures were extracted from healthcare records and national registers.

Weight, length and body mass index (BMI) at birth were inversely associated with the presence of frailty in both sexes. Men who were frail in old age had experienced accelerated BMI gain from the age of 2 to 11 years compared to non-frail men. Similarly, men who as boys experienced wartime separation from both parents were at an increased risk of frailty compared to non-frailty. No similar associations were observed in women. Those who worked in manual labor occupations as adults were at an increased risk of frailty compared to those who worked as officials. Short leukocyte telomere length at the mean age of 61 years was associated with frailty at the mean age of 71 years. Furthermore, frail individuals had shorter telomeres at the mean age of 71 years compared to non-frail individuals. No association between telomere shortening and frailty was observed.

Several life-course determinants of frailty were identified. Associations between factors taking place during gestation and early life suggest that susceptibility to frailty may be programmed early in life. Moreover, the association between BMI growth and wartime separation and frailty may vary by sex. Leukocyte telomere length may be a meaningful frailty biomarker in its ability to detect processes that are associated with frailty. The prevention of chronic disease and frailty should start already at a young age e.g. through the promotion of the health of mothers in childbearing age.

TIIVISTELMÄ

Yli 60-vuotiaiden osuuden väestöstä ennustetaan tuplaantuvan 24 prosenttiin vuoteen 2050 mennessä. Gerastenian (suom. ger=vanha ja astenia=heikkous) vallitsevuus kasvaa voimakkaasti ikääntymisen myötä, ja sitä luonnehtivat alentuneet biologiset voimavarat sekä heikentynyt vastustuskyky stressitekijöille useassa elinjärjestelmässä. Gerastenisen henkilön edellytykset palautua stressitekijän jäljiltä ovat alentuneet, ja gerastenia on yhteydessä ei-toivottuihin terveystapahtumiin, kuten sairaalajaksoihin ja ennenaikaiseen kuolleisuuteen. Tehokas gerastenian ehkäisy edellyttää tietoa sen riskitekijöistä. Terveyden ja sairastavuuden kehityksellistä alkuperää tarkasteleva DOHaD-hypoteesi korostaa varhaisen elämän merkitystä aikuisiän sairastuvuuteen. Aikaisemmissa pitkittäistutkimuksissa on havaittu yhteyksiä varhaiselämän altistusten ja kansansairauksien, kuten sydän- ja verisuonisairauskien ja tyypin 2 diabeteksen, välillä. Tutkimuksen tavoite oli tutkia gerasteniariskiä elämänkaaren näkökulmasta.

Tutkimus on Helsingin syntymäkohorttitutkimuksen osatutkimus, ja siihen sisältyy 8760 Helsingissä vuosina 1934–1944 syntynyttä henkilöä. 2902 satunnaisesti kutsutusta henkilöstä 2003 osallistui kliiniseen tutkimukseen vuosina 2001–2004. Heistä 1,404 kutsuttiin jatkotutkimukseen, johon osallistui 1094 henkilöä vuosina 2011–2013. Gerastenia määritettiin seurantatutkimuksen yhteydessä keskimäärin 71 vuoden iässä käyttäen Friedin fenotyyppimääritelmää. Tieto elämänkaaren aikaisista riskitekijöistä saatiin terveydenhuollon asiakirjoista ja kansallisista rekistereistä.

Syntymäkoko oli kääntäen verrannollinen gerasteniariskiin. Gerasteniset miehet kasvoivat muista miehistä poiketen: lapsuudessa heidän painoindeksinsä kasvoi nopeammin 2-11 ikävuoden aikana ei-gerastenisiin miehin verrattuna. Samoin miehet, jotka olivat lapsuudessaan sotalapsia, sairastuivat useammin gerasteniaan keskimäärin 71 vuoden iässä. Vastaavia yhteyksiä ei havaittu naisten keskuudessa. Aikuisiässä tehdastyötä tehneillä oli lisääntynyt riski gerasteniaan. Niillä henkilöillä, jotka olivat gerastenisia keskimäärin 71 vuoden iässä, oli keskimäärin lyhyempi telomeeripituus 61 ja 71 vuoden iässä. Yhteyttä telomeerien lyhenemisen ja gerastenian välillä ei sen sijaan havaittu.

Tässä väitöstutkimuksessa tunnistettiin useita elämänkaaren aikaisia riskitekijöitä gerastenialle. Yhteydet varhaisen elämän ja gerastenian välillä viittaavat, että alttius gerasteniaan voisi syntyä jo varhain elämässä. Kasvun ja sotalapsuuden yhteys gerasteniaan voi sen sijaan olla sukupuolesta riippuvainen. Valkosolujen telomeeripituus saattaa olla hyödyllinen gerastenian biomarkkeri johtuen sen kyvystä havaita gerastenialle altistavia prosesseja. Kroonisten sairauksien ja gerastenian ennaltaehkäisyn tulisi alkaa jo varhaisemmalla iällä esimerkiksi tukemalla raskaana olevien äitien terveyttä.

SAMMANFATTNING

Andelen över 60-åriga personer förutspås fördubblas och uppgå till 24% år 2050. Gerasteni är en geriatrisk sjukdom som innebär att individen inte har tillräckliga förutsättningar för återhämtning från små förändringar i hälsotillståndet på grund av nedsatt stresstolerans i flera organsystem. Gerasteni, som blir allt vanligare med tilltagande ålder, karakteriseras av en ökad risk för sjukhusvård samt ökad dödlighet. Ökad kunskap om riskfaktorer för gerasteni kan möjliggöra prevention av sjukdomen. Enligt DOHaD-hypotesen kan förhållanden under det tidiga livsskedet påverka den framtida hälsan i stor utsträckning. Longitudinella studier har påvisat att kroniska sjukdomar så som kranskärlssjukdom och typ 2 diabetes har riskfaktorer som härstammar från spädsbarnsålder och tidig barndom. Avhandlingens syfte var att studera gerasteni ur ett livcykelperspektiv.

Denna delstudie av Helsingfors födelsekohortstudie inkluderar 8760 individer som föddes i Helsingfors under åren 1934–44. Av de 2902 slumpmässigt inbjudna deltog 2003 i en klinisk studie under åren 2001–2004. Sammanlagt 1404 individer kallades till en uppföljningsstudie under åren 2011–2013 varav 1094 deltog. Gerasteni definierades enligt fenotypmodellen i medeltal vid 71 års ålder. Information om tidiga riskfaktorer för gerasteni erhölls ur nationella hälsovårdsregister samt andra register. Information erhölls även från de kliniska undersökningarna.

Ett omvänt förhållande mellan vikt, längd och BMI vid födseln å ena sidan och å andra sidan gerasteni konstaterades. De gerasteniska männen upplevde en annorlunda tillväxt i barndomen än de övriga männen: deras viktindex ökade snabbare än viktindexet bland de icke-gerasteniska männen från 2 till 11 års ålder. De män som i barndomen varit krigsbarn insjuknade oftare i gerasteni. Inga liknande samband hittades bland kvinnorna i studien. En lägre socioekonomisk ställning i vuxen ålder var förknippad med en ökad risk för gerasteni. Individer som var gerasteniska vid 71 års ålder hade kortare telomerlängd vid 61 och 71 års ålder jämfört med dem som inte var gerasteniska. Inget samband mellan telomerförkortning och gerasteni konstaterades.

Flera tidiga riskfaktorer för gerasteni konstaterades i studien. Sambandet mellan olika faktorer i det tidiga livsskedet och gerasteni i ålderdomen påvisar att risken för gerasteni kan programmeras redan tidigt i livet. Den tidiga tillväxtens och stressens inverkan förefaller vara olika hos män och kvinnor. Telomerlängden kan vara en meningsfull biomarkör för gerasteni. Man borde redan i ett tidigt livsskede börja förebygga kroniska sjukdomar och gerasteni t.ex. genom att stöda hälsan hos gravida kvinnor.

1 INTRODUCTION

Globally, the mean ages of populations are increasing. The fastest growing age group is those aged 60 and older, whose proportion of the global population is expected to double from 12 % to 24 % by the year 2050. With decreasing fertility and increased longevity many developed nations are facing an ageing crisis. (1)

Frailty, a geriatric syndrome of which the prevalence increases from 3.2 % at the age of 65-70 years to 16.3 % at the age of 80-84 years when Fried frailty phenotype criteria were used (2), constitutes a major challenge to ageing societies worldwide (3). Frailty, according to the Fried criteria, can be defined as the presence of three or more of the following criteria: *exhaustion, weight loss, weakness, low physical activity* and *slowness* (2). Frail individuals fail at recovering from minor changes in their health status due to decreased physiological reserves across several organ systems (2,4). Consequently, they are at increased risk of adverse health outcomes including falls, fractures, hospitalization, disability, nursing home admission and premature mortality (5–10).

Prevention of frailty has been a public health priority for several ageing societies (11). Effective frailty prevention requires knowledge on its risk factors. Several adulthood risk factors of frailty, including older age, obesity, smoking, polypharmacy, multimorbidity and poor cognitive and physical functioning, have been identified (2,12–14). The understanding of complex ageing-associated diseases, however, requires a life-course approach (15,16).

Life-course epidemiology studies the long-term associations between exposures that take place during gestation, childhood, adulthood and health in later life (17). Few studies have investigated frailty from a life-course perspective and little is known about its early life origins. Previous studies have shown that factors which the individual is exposed to *in utero* and early infancy were associated with chronic diseases including cardiovascular disease and type 2 diabetes through a phenomenon known as 'programming' (18–21). Exposures that take place during sensitive phases in development can have permanent and long-lasting effects on later health. For example, rats that were exposed to undernutrition during gestation were smaller, grew slower and aged faster than rats that were not exposed to undernutrition *in utero*. (22)

The present study aims at studying frailty from a life-course perspective in the Helsinki Birth Cohort Study among 1,078 individuals born in 1934-1944. We investigated associations between factors and exposures taking place during gestation, childhood, adulthood and later life and frailty at the mean age of 71 years.

2 REVIEW OF THE LITERATURE

2.1 DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Evidence from animal studies suggests that exposures taking place during critical phases in development may have long-lasting and even lifelong effects on later health. When a female rat was injected with testosterone on the 5th day after birth, development continued normally until puberty. In puberty, these rats failed to ovulate and express normal sexual behavior due to irreversibly altered function of the hypothalamus. When testosterone was injected to female rats on the 20th day after birth, no similar effects were observed, and the rats expressed normal sexual behavior (23). The experiment suggested that development of reproductive traits could be permanently changed during sensitive periods in development. Another example from rodents is the observation of accelerated aging in rats undergoing undernutrition *in utero*. Rats that were exposed to undernutrition *in utero* and up to three weeks after birth experienced on average a more rapid progression in albuminuria and other aging-related physiological changes than rats that received adequate nutrition (24). Moreover, in another experiment where rats were exposed to undernutrition *in utero* but then given adequate nutrition in postnatal life, a significant reduction in their lifespans was observed (25).

A study published in The Lancet in 1986 showed that ischaemic heart disease (IHD), which had gradually become more prevalent with increasing prosperity and quality of life, was not nearly as deadly for others as for some (26). By comparing infant mortality rates in England and Wales in 1921-1925 to mortality rates from IHD in the same areas in 1968-1978, David Barker and colleagues were able to point out that the areas where more people died of IHD had had higher than average infant mortality rates some half a century earlier. They suggested that it was malnutrition that occurred early in life which predisposed some individuals to the harmful effects of a diet associated with affluence and IHD. A few years later, findings from a cohort of 5,654 men born in Hertfordshire, England, between 1911 and 1930, showed that lower than average size at birth and at 1 year of age were associated with increased mortality from IHD. Combined small size at birth and at 1 year were associated with highest mortality from IHD. (27)

The role of lifestyle-related factors in chronic disease pathogenesis was known during those times. With passing years, the findings of Barker and colleagues were confirmed in other populations and extended to include other determinants and outcomes. As a result, the *Foetal Origins Hypothesis,* or the *Barker Hypothesis,* was born. The hypothesis states that foetal undernutrition that takes place during critical phases of gestation may result in abnormal growth of the foetus, and through permanent changes in the newborn, affect

adult chronic disease risk (28). Further research suggested mediating and independent effects of events occurring at sensitive periods after the foetal period, primarily in infancy and childhood. The Developmental Origins of Health and Disease (DOHaD) hypothesis examines adult disease from the perspective of all of development and related sensitive periods.

A central part of the DOHaD hypothesis is programming (21). Developmental plasticity refers to the ability of the developing foetus to pick up subtle cues from the environment during critical periods in development. These cues serve as important predictors of the postnatal environment, and by being plastic, the foetus may facilitate changes to its biology to better adapt to this environment. These changes are often irreversible and cannot be modified outside of critical phases in development. (29,30) A match between intrauterine conditions and those encountered later in life would result in beneficial adaptive changes and increased survival. However, in contemporary conditions where food has become more available to humans worldwide, a predicted postnatal life of limited nutrition is less frequently matched. This results in the mismatch of pre- and postnatal conditions. This mismatch could facilitate changes in biology that may, in the long term, lie on the pathway to chronic disease. (19)

The mechanisms by which the foetus is programmed are complex and likely to involve changes in hormonal, metabolical and physiological systems (Figure 1). Interactions between the environment and foetal genes may result in epigenetic changes in which gene expression is altered without modifying the deoxyribonucleic acid (DNA), with effects observed to extend over several generations. Results from experiments done with animals stress the importance of timing, intensity and duration of stressors in determining their significance (31). For example, when the foetus is challenged during a period of maternal caloric restriction, growth of vital tissues e.g. the brain is prioritized over those in skeletal muscle and kidneys (32). Similarly, growth retardation can be induced by hypoxic conditions in high altitudes (33) or by carbon monoxide as the result of cigarette smoking (34).

Other maternal factors such as high levels of stress and oral use of glucocorticoids have been found to influence hormonal pathways of the foetus, namely that of the hypothalamus-pituitary-adrenal (HPA) axis, through increased levels of circulating hormones. These circulating hormones have been suggested to modify organogenesis, receptor regulation and sensitivity to feedback mechanisms in not only the HPA axis but also in other parts of the body. Alterations in DNA methylation, expression of regulatory genes and noncoding ribonucleic acid (RNA) molecules have been targeted as possible pathways to modify the foetal epigenome. (35) Furthermore, other hormones including growth hormone, insulin-like growth factors (IGFs), thyroid hormones as well as those secreted by the placenta have been suggested to be involved, although to a lesser extent (36).

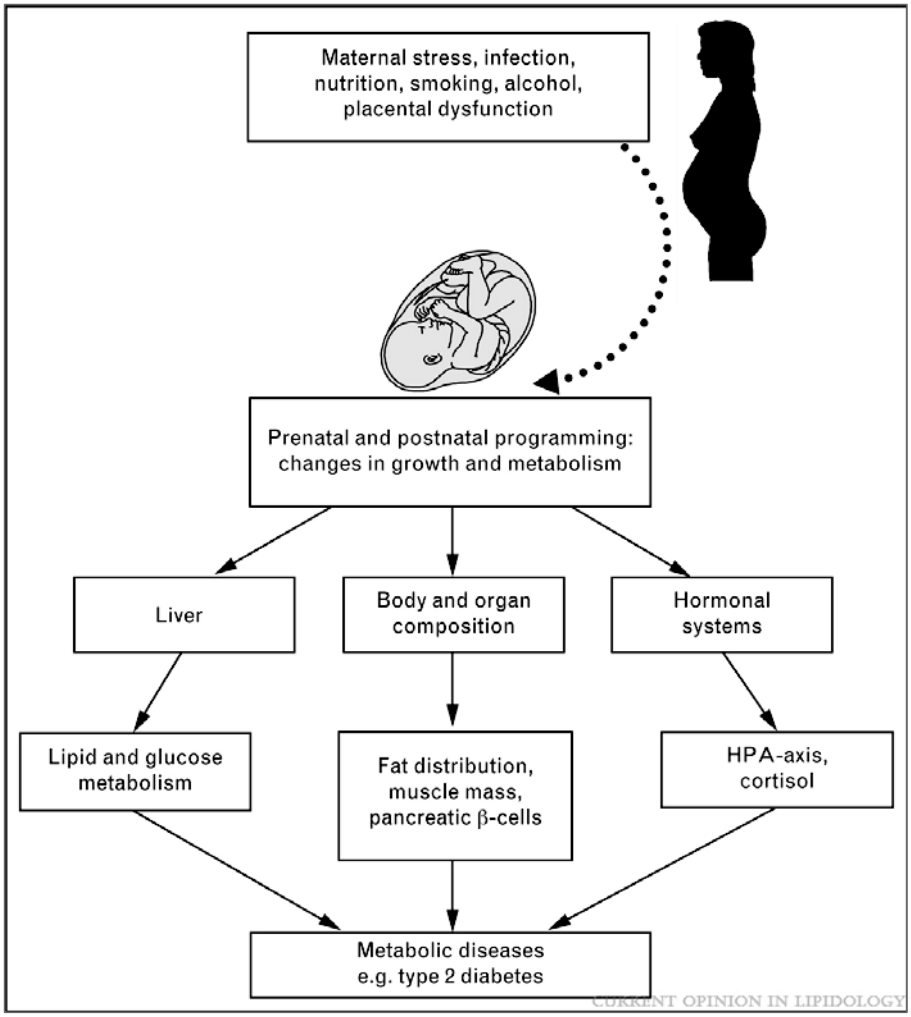

Figure 1 Pathways of programming of later disease susceptibility, reproduced with permission from copyright holder (37).

2.2 BODY SIZE AT BIRTH

Body size at birth, and birth weight in particular, have been considered to be crude markers of the intrauterine environment in adult cohorts that have limited data on foetal growth. The universality and high recall rate together with documented low recall bias support the use of birth weight in epidemiological studies (38,39).

Studies examining the association between birth weight and outcomes in neonates and infants report that children born below a certain size are at increased risk of health difficulties and premature mortality. Furthermore,

rather than being linear, this risk has been described to increase exponentially with decreasing birth weights. The World Health Organization (WHO) has defined 'low birth weight' as measured weight at birth that is below 2500 grams. (40)

Several factors which are known to affect birth weight have been identified, summarized in Figure 2. Mothers of short stature and smaller size give birth to smaller babies. Toxins such as cigarette smoke or alcohol, and deprivation of nutrients e.g. during maternal undernutrition, have been associated with smaller birth weight. Nutrients are transported to the developing foetus through the placenta and disturbances in its function can also affect nutrient intake of the foetus. The parents' genetic information is transferred to the foetus, which has its own unique genotype. Gene-environment interactions, in which altered gene expression may occur without changes to DNA itself, may affect birth weight through epigenetic signalling. (40,41)

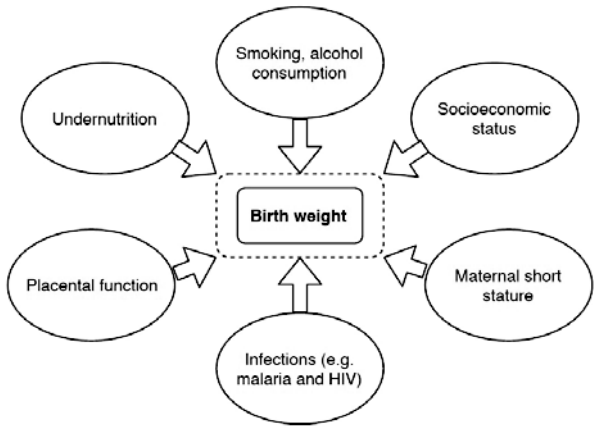

Figure 2 Factors associated with decreased birth weight (40,41).

2.2.1 BODY SIZE AT BIRTH AND ADULT DISEASE

The original findings of Barker and colleagues linking low birth weight with later IHD (27) have since been extensively replicated in cohorts worldwide (42–48). A meta-analysis of studies on birth weight and later coronary heart disease (CHD) risk suggested that per each 1 kg increase in birth weight the relative risk of CHD was reduced by 10-20 %, and that being small at birth (birth weight <2500 g) would increase later CHD risk (49). Birth size has been linked with several non-communicable diseases in adulthood (Table 1).

Small birth weight has since been associated with risk factors for CHD. An inverse relationship between birth weight and systolic blood pressure (SBP) in adulthood (50) was later extended to include low birth weight as a risk factor for hypertension in both men (51) and women (52). Results from a meta-analysis of 31 studies suggest that while hypertension is more prevalent among

children with high birth weight, this trend is reversed in adulthood and later life, showing a protective effect from hypertension in adulthood among those who had higher birth weight (53). Evidence from studies assessing the association between birth weight and stroke risk suggest that a low birth weight may result in increased subsequent risk of stroke (44,47,54,55).

The association between birth weight and diabetes has been studied in several cohorts. Initially an inverse association between birth weight and type 2 diabetes (20,51,56,57) has since been extended to include both extremes, resulting in a U-shaped association between birth weight and the risk for type 2 diabetes (58). Conversely, high birth weight alone was found to be associated with type 1 diabetes in a meta-analysis of 12 cohorts (59). Similarly, high birth weight has been associated with a higher prevalence of adult obesity (52,60) and autoimmune diseases including rheumatoid arthritis (61,62) and Sjogren's syndrome (63).

Low weight at birth has been associated with mental health disorders such as depression in adulthood (64). Although with varying heterogeneity, this has also been replicated in more recent meta-analyses (65,66). Furthermore, evidence from meta-analyses report on associations between low birth weight and chronic diseases and conditions such as asthma (49), decreased lung function (67), decreased bone mineral content (BMC) (68,69) and chronic kidney disease (70,71).

The role of birth weight in determining subsequent cancer risk may depend on tumour type. While low birth weight has been found to be associated with an increased risk of testicular cancer (72), high birth weight has been found to be associated with malignancies of the breast (73), prostate (74) and bone marrow (75) in meta-analyses of observational cohorts. Mortality from all causes was greater in those with births weights of 2500 grams or less than those with a normal birth weight. Low birth weight has been associated with mortality from cancer in men but not among women. (76)

Table 1. *Birth weight and examples of some associated conditions*

Low birth weight	High birth weight
Coronary heart disease	Obesity
Cerebrovascular disease	Type 1 diabetes
Hypertension	Type 2 diabetes
Type 2 diabetes	Certain cancers
Depression	Certain autoimmune diseases
Obstructive pulmonary disease	
Osteoporosis	
Chronic kidney disease	
Certain cancers	
All-cause mortality	

2.2.2 BODY SIZE AT BIRTH AND FRAILTY

No previous studies assessing associations between measures of size at birth and walking speed, exhaustion and weight loss were found. However, studies that have examined the association between birth weight and leisure time physical activity (LTPA) in late adulthood (77–79) report a trend of lower LTPA in groups with the lowest birth weight. However, birth weight was not associated with LTPA in a study focusing on strenuous LTPA in midlife (80). A meta-analysis including 13 studies suggested strong associations between extremes of both low and high birth weight and decreased LTPA but very weak associations in birth weights that were considered to be within normal range (81).

Similarly, a positive association between birth weight and grip strength in early (82–85) and late adulthood (86–88) has been observed. Furthermore, a study that assessed birth weight and longitudinal grip strength trajectories found that men born small reached a lower peak grip strength in midlife (89). Results from a meta-analysis showed positive associations between birth weight and grip strength measured at many points during life (90).

The association between birth weight and frailty has been assessed in the Dutch famine cohort. In that study, a graded yet non-significant trend of decreasing birth weight with increasing frailty classification was observed. With few frail individuals the study lacked in statictical power. (91) Moreover, a study assessing hereditary and environmental frailty determinants among 1,642 twin pairs aged 40-84.5 years showed that age and birth weight contributed to 11.9% of the variance in the used frailty definition. However, in this study of twins, birth weight was self-reported (range 0.793 to 4.129 kg) and, on average, low (mean 2.382 kg). (92)

2.3 INFANT AND CHILDHOOD GROWTH

Infancy refers to the period of rapid growth and development ranging from birth to the approximate age of 2 years. Following infancy, childhood spans the ages of 2 to 11 years. Both infancy and childhood include different developmental milestones and mechanisms (93).

Adiposity increases in early infancy and decreases in childhood. In early childhood, within the approximation of ages 5 to 7 years, adiposity starts to increase again. The age at which adiposity starts to increase in childhood, termed as ‘adiposity rebound’ or ‘body mass index (BMI) rebound’, is important in predicting adiposity in adult life. Those who experience adiposity rebound earlier have on average higher adiposity in adulthood. (94) In the Helsinki Birth Cohort Study (HBCS), the cumulative incidence of type 2 diabetes in adulthood was observed to be higher among those experiencing BMI rebound before the age of 5 years (8.6%) than for those in whom it occurred at the age of 7 years or later (95).

2.3.1 EARLY GROWTH AND ADULT DISEASE

While prenatal exposures are important factors in influencing later health, they may to some extent be modified by postnatal growth. The human body is highly adaptable to changes in the environment, but when these circumstances become highly polarized, they become 'mismatched'. For example, undernutrition in utero may result in changes to metabolism that aim to optimize the use of nutrients in later life. However, facing excess nutrition, these mechanisms may not be beneficial and result in accelerated growth in body size. (19) Size at birth and patterns of postnatal growth have been linked with certain adult disease (Table 2).

In the HBCS, those men who as adults were admitted to hospital due to coronary artery disease (CAD) had on average been small at birth and remained small until the age of 2 years, after which they rapidly grew in weight and BMI reaching the cohort average by the mean age of 11 years. In the same study cohort, a similar finding was also observed in women. The women also remained small in the first 2 years of life, but in childhood they caught up faster with the rest of the cohort, finally being above the cohort average in weight and BMI by age 11 years. (18)

The pattern of growth which has been associated with adult hypertension closely resembles that of CAD. Participants with previously diagnosed hypertension (for example for receiving state reimbursement for hypertension medication) had been small at birth and they had experienced little change in mean Z-scores for height and weight until the age of 2 years. By the age of 11 years, they had caught up with the rest of the cohort in weight, height and BMI. A different pattern of growth was identified in participants with newly-diagnosed hypertension. Those with mean systolic blood pressures of 140 mmHg or higher or diastolic blood pressures of 90 mmHg or higher at the examination had not been small at birth but after birth their average weight, height and BMI fell below the cohort average and remained below average throughout childhood to the age of 11 years (96). A similar pattern of growth has been linked with a higher stroke incidence (97). In boys with average or high birth weight, growth-velocities for BMI and height between 8 to 13 years were associated with hypertension at the mean age of 51 years, whereas no associations between childhood growth and hypertension were observed among girls (98). In individuals aged 26-32 years from Delhi, India, rapid BMI gain from birth to the age of 11 years was associated with elevated blood pressure levels in adulthood (99).

Certain patterns of growth have also been associated with metabolic diseases. A pattern of accelerated BMI and weight gain compared with the cohort mean from birth to the age of 11 years was associated with obesity and the metabolic syndrome at age 26 to 32 years in the New Delhi cohort (99). In a cohort of Finns, participants who developed the metabolic syndrome had weighed less at birth and were thinner from birth to 7 years of age (100). In a cohort of Indians aged 26 to 32 years, those who had developed impaired glucose tolerance (IGT) or type 2 diabetes by the age of 32, had on average had

a low BMI until the age of 2 years but had then caught up in BMI by the age of 12 years (101). Again, those with a low BMI at the age of 1 to 4 years followed by high BMI were observed to be at an increased risk of IGT or diabetes in adult life (99). Among older Finnish participants, those who later developed type 2 diabetes had been small at birth, caught up with the others by the age of 7 years, and between the ages of 7-15 years, experienced accelerated weight gain (20).

Patterns of growth have also been linked with impairments in lung function, decreases in BMC and prevalent depressive symptoms (102–105). In terms of mortality, differences in patterns of growth have been observed among men and women. While an increase in all-cause and cancer mortality was observed among women who as girls experienced accelerated BMI growth, men with higher cancer mortality rates tended to have retarded BMI growth in childhood. (106)

Table 2. *Size at birth and postnatal growth on examples of some adult conditions*

	Size at birth		
Accelerated growth	**Small**	**Average**	**High**
In infancy (approx. 0-2y)			
In childhood (approx. 2-11y)	Coronary artery disease Hypertension Metabolic syndrome Obesity Impaired glucose tolerance Type 2 diabetes		
In adolescence (11y and older)	Type 2 diabetes All-cause and cancer mortality (women)		Hypertension (men)
Deccelerated growth			
In childhood (approx. 2-11y)		Hypertension Stroke Cancer mortality (men)	

2.3.2 EARLY GROWTH AND FRAILTY

There are currently no previous studies that have reported findings on early growth and frailty. However, studies have explored associations between early growth and some of the frailty criteria. Findings regarding the association between postnatal growth and later grip strength have not been consistent in men and women. Accelerated weight gain during the first year of life was found to be associated with better grip strength in young (107) and older men (108). Bigger body size at ages 2 (weight for length z-score) and 4 years (height for age z-score) was associated with better grip strength more consistently among men than women. Furthermore, these associations were observed to be mediated by adult lean mass (85). In another study, 1-standard deviation increases in height growth velocities between the ages of 2 and 7 years were associated with better grip strength in both sexes combined, whereas between the ages of 7 and 15 years, 1-standard deviation increases in weight gain velocities in men and height gain velocities in women were associated with better grip strength at the mean age of 53 years (109).

No studies were found which assessed the association between early growth and later walking speed. However, some studies assessing the effects of early growth on later physical performance and functioning included components of walking distance and physical activity in their composite outcome variables. While conditional infant growth was not associated with physical performance in one study (110), another study using the physical functioning sub-scale of the Short Form 36 survey reported an association between infant growth and better physical functioning score at the mean age of 61 years (111). In contrast, other studies have reported associations between early growth and physical performance in men (112) and for both sexes combined (113). No studies on early growth and other frailty criteria including exhaustion and weight loss were identified.

2.4 EARLY LIFE STRESS

Stress has been defined as “a state in which homeostasis is actually threatened or perceived to be so [and] homeostasis is re-established by a complex repertoire of behavioural and physiological adaptive responses of the organism” (114). Evidence from animal studies suggests that early exposure to either stress or glucocorticoids may result in reprogramming of the HPA-axis, and altered neurodevelopment, cognition and mental health (115–118). Early life stress (ELS) includes these changes to homeostasis that occur within the timeframe from early gestation to puberty due to either social, psychological or physical events (119).

In humans, early life stressors may include maternal factors such as intake of exogenous glucocorticoids or infections (120), factors involving the child’s living environment such as maltreatment or abuse (121,122), or tragic life

events in childhood including the loss of a parent through divorce or death (123,124).

2.4.1 EARLY LIFE STRESS AND ADULT DISEASE

Mental health and well-being are among the most studied outcomes of ELS. Former Finnish war evacuees, who had been evacuated to Sweden or Denmark as children during World War II (WWII), reported significantly more severe depressive symptoms in the 6th decade of their life than those who had not been evacuated (125). Among former British WWII evacuees, poor foster care was associated with depression in old age (126). Furthermore, wartime separation has been associated with later risk of severe mental health disorders, namely substance misuse and personality disorders (127,128), and in general, former war evacuees report lower levels of psychosocial well-being than non-evacuees (129). Poor mental health and reduced mental health related quality of life in adulthood have been associated with neglect and abuse in childhood (130,131).

Evidence suggests that ELS may affect later health behavior. Self-reported adverse childhood experiences were associated with alcoholism, drug abuse, smoking, physical inactivity, depression and suicide attempts in a sample of the U.S. population aged 19-92 years (132). Similarly, associations between adverse childhood experiences and obesity (132,133) and chronic pain (134) have been reported.

Children who had been subjected to abuse or maltreatment reported lower levels of physical health and quality of life in later life (130,131,135). Furthermore, those who reported having had adverse childhood experiences had higher rates of cardiovascular disease (CVD) as adults than those who did not (132,134,136), even after adjusting for other risk factors for CVD (137). Similarly, the prevalence of CVD has been observed to be greater among former war evacuees than non-evacuees (138,139). Moreover, childhood wartime experiences have been linked with later blood pressure levels (138,140,141).

Childhood neglect has been associated with an increased risk of diabetes in adulthood (136). Furthermore, a higher prevalence of diabetes has been observed among those experiencing childhood adversities than among those who reported no childhood adversities (134). Among former war evacuees, those who had been separated from both parents during WWII were more frequently diagnosed with type 2 diabetes compared to those who had not been separated (138). Besides diabetes, ELS has been associated with a number of other diseases including pulmonary disease, bowel disease, liver disease, arthritis and cancer (132,134,136,142,143).

2.4.2 EARLY LIFE STRESS AND FRAILTY

There is little evidence on the association between ELS and frailty or frailty criteria. In a cross-sectional study of 2,002 individuals aged 65-74 years where information on self-reported childhood physical abuse and frailty was available, a higher proportion of frail (17.8%) than non-frail (9.7%) participants reported having experienced physical abuse in childhood. In that study, childhood physical abuse was associated with frailty in the crude model but was attenuated after adjustment for covariates including age, gender, education and study site. (144)

2.5 TELOMERE LENGTH

During somatic cell division, replication of the two DNA strands is initiated by DNA polymerase, an enzyme that requires RNA primers with 3' hydroxyl groups paired to the template strand. As DNA polymerase moves along to replicate the DNA, the RNA primers are discarded. This leaves a gap of missing genetic information at the ends of the newly built DNA, which in the absence of telomeres would lead to loss of genetic material with each cell division. (145)

Telomeres are tandem TTAGGG repeats located at the ends of eukaryotic chromosomes. Their structure, a protein complex, is dynamically assembled and disassembled in cycles. The primary function of telomeres and associated enzymes is to maintain chromosomal integrity by enabling full replication of the DNA strands. Instead of chromosomal DNA, some of the repeat sequence of the telomere is lost with each somatic cell division. In contrast, the enzyme telomerase can add new repeats to the telomere. When the telomeres are critically short, the cell no longer proliferates thus entering senescence, and ultimately, apoptosis. (146)

Disparities in telomere length begin from as early on as in the womb as the result of various environmental and genetic factors. Consequently, variability in leukocyte telomere length (LTL) can be already detected at birth. (147) After birth, it is suggested that LTL undergoes rapid shortening until the 2nd decade after which this rapid shortening slows down (148–150). A recent study of 4 longitudinal cohorts studying age-dependent shortening of LTL across six decades of adult life suggested that the rate of LTL shortening would be relatively stable during adulthood and that differences in the rates at which LTL shortens would mostly be attributed to factors that originate early in life (151). Among adults and older individuals, women have consistently been reported to have longer LTL, and during a given period, women experience less of telomere shortening than men (152,153). Male sex, smoking and physical inactivity have been associated with shorter telomere length, and variation in telomere length has also been observed across different ethnic groups (154).

2.5.1 METHODOLOGY TO MEASURE TELOMERE LENGTH

The availability of peripheral blood leukocytes in blood samples, high quality of their DNA and the notion of correlation of leukocyte telomere length attrition across tissue types (155) make leukocytes attractive cells for measuring telomere length. Since the first telomere measurement in the year 1988 utilizing DNA sequencing (156), many methods have been introduced (157).

Terminal restriction fragment (TRF) analysis utilizes 'TTAGGG'-labelled probes in detecting telomeric regions, which can be run through gel electrophoresis and Southern blot analysis (158,159). TRF analysis gives average LTL's in kilobases. However, large amounts of DNA are required and performing of the assays can be time consuming and moreover, inclusion of other areas than the actual telomeres, or the use of enzymes, may affect measurement results.

The polymerase chain reaction (PCR) method is widely used in epidemiological studies due to its high throughput, low requirement of sample DNA and low cost. The method measures the proportion of telomere signals (T) to a single-copy gene signal (S) that acts as a reference, giving relative measures of telomere length, as T/S-ratios rather than absolute telomere length in kilobases (160,161). Drawbacks of the PCR method include higher coefficients of variation than with the TRF method and inability to capture lengths of the shortest telomeres (157).

2.5.2 TELOMERE LENGTH AND ADULT DISEASE

As a surrogate marker of cellular lifespan, short LTL has been shown to be associated with a range of clinical conditions, presented in Table 3. Mutations in areas that normally generate functioning telomere complexes may result in pathologic disease states including bone marrow failure, dyskeratosis congenita, acquired aplastic anemia and pulmonary fibrosis (162).

The role of short LTL in chronic disease pathogenesis has been studied extensively. Short LTL has been associated with increased thickness of the intima of the carotid artery (163), carotid atherosclerosis (164) and CAD (165,166). Among individuals with established CAD, short LTL was associated with better responsiveness to conventional statin treatment than did longer LTL (165). Short LTL has been associated with premature myocardial infarction (167) and mortality among patients with CAD (168) whereas no association between LTL and incident atrial fibrillation has been observed (169).

Compared to controls with normal glucose regulation, shorter LTL has been observed among those with IGT (170) and type 2 diabetes (171,172). Short LTL has also been linked with incident type 2 diabetes in some (173,174) but not all studies (175). Similarly, short LTL has been associated with a higher body fat percentage and subcutaneous fat but not with other related measures

of body composition including the amount of visceral fat and overall BMI (176).

Telomere biology has been suggested to play an important role in the development of some cancers (162). Meta-analyses of observational studies suggest an increased overall cancer risk among individuals with short LTL and that this risk would further be elevated in certain types of cancers including those of the bladder, lung and digestive system (177,178). However, an association between long LTL and melanoma risk has also been reported (179).

Besides cellular lifespan, LTL has also been linked with the human lifespan showing an increased all-cause mortality risk among individuals with short LTL (180,181). This association has been shown to vary according to ethnicity (182). However, some studies report no association between LTL and mortality (183).

Table 3. *Examples of diseases which have been associated with short LTL*

Condition
Coronary artery disease[1,2]
Type 2 diabetes[3,4]
Myocardial infarction[5]
Heart failure[6]
Obstructive pulmonary disease[7,8]
Gastrointestinal disease[9,10]
Alzheimer's dementia[11,12]
Parkinson's disease[13]
Certain autoimmune diseases[14,15]
Certain cancers[16,17]

Note. [1](165), [2](166), [3](173), [4](174), [5](167), [6](184), [7](185), [8](186), [9](187), [10](188), [11](189), [12](190), [13](191), [14](192), [15](193), [16](177), [17](178)

2.5.3 TELOMERE LENGTH AND FRAILTY

Evidence on the associations between LTL and frailty criteria is not consistent. In a study of older twins, individuals in the category with the highest LTPA had on average longer LTL compared to those in the category with the lowest LTPA, and among twins, the more active twin often had longer LTL than the less active twin (194). Among older African American and white women, women exceeding the recommendation of LTPA had significantly longer LTL than women who were the least active (195). In a study of older business executives, moderate LTPA was associated with long LTL at the follow-up, and LTLs of groups with either high or low LTPA had on average shorter LTL than that observed for those in the moderate LTPA group (196).

Evidence from cross-sectional studies suggest an association between longer LTL and better grip strength among older individuals (197) and that

this association may vary by sex (198). However, grip strength at the mean age of 31 years was not associated with LTL (199). When it comes to walking speed, most (197,198) but not all (200) studies found no association between LTL and walking speed. No studies assessing associations between weight loss, exhaustion and LTL were identified.

Studies investigating the association between LTL and frailty have provided contradictory results. In studies defining frailty according to the criteria put forward by Fried (201–203), Rockwood (204–206) or both (207,208), no associations between LTL and frailty were observed. On the other hand, an increasing body of literature also suggests the opposite; short LTL was associated with frailty according to Fried (209) and with a definition of frailty composed of information from laboratory measurements only (210).

2.5.4 TELOMERE SHORTENING AND ADULT DISEASE

Studies of telomere shortening and adult health involve longitudinal study settings where several LTL measurements are available for individual participants. In a recent study of men and women aged 31-76 years, telomere shortening was not associated with carotid atherosclerosis during a 9.5-year follow-up (164). Among patients with heart failure, telomere shortening was not associated with incident mortality or hospitalization due to heart failure (211). When telomere shortening and the metabolic syndrome were studied, no associations were observed; however, a greater increase in waist circumference was associated with accelerated telomere shortening (212). Similarly, weak associations between increases in waist circumference and accelerated telomere shortening were observed (213). Furthermore, an association between shortening of telomeres in pancreatic β-cells during a 10-year follow-up and diabetes has been reported (214).

Telomere shortening may not be involved in the disease progression of obstructive pulmonary disease, depression and anxiety disorders (215–217). However, greater telomere attrition has been associated with changes to the central nervous system, namely the loss of hippocampal volume and changes to the fornix (218). Telomere shortening during a 13-year follow-up period was observed to be associated with poorer global cognition in individuals aged 48-52 years (219). In a study of 1,356 individuals aged 30-70 years, telomere shortening was not associated with all-cause mortality over 10 years of follow-up (220).

2.5.5 TELOMERE SHORTENING AND FRAILTY

Currently there are no available studies that report associations between LTL shortening and frailty. In the Hertfordshire cohort, telomere shortening and grip strength, which is used in determining the frailty criterion of weakness, were studied across 10 years of follow-up. An association between greater telomere shortening and decreased grip strength at the follow-up was

observed, however, these results were attenuated after controlling for inflammatory markers. In that study, measurements related to determining the criteria of slowness (walking speed from a 6-minute walking test) and low physical activity (LTPA, self-reported physical performance) were also available, showing no associations between the 6-minute walking test, self-reported physical performance and telomere shortening. (221)

Telomere shortening was not associated with walking speed or grip strength in adults aged 53-80 years with a follow-up ranging from 7.5 to 10.2 years (197). In two subsets of the Lothnian birth cohort, changes in telomere length were not associated with changes in walking speed (6-minute walking test) and grip strength (222). No studies assessing telomere shortening and the criteria of weight loss and exhaustion were identified.

2.6 FRAILTY

Frailty is a geriatric syndrome that is characterized by the loss of biological reserve and resistance to stressors across several organ systems due to accelerated and cumulative ageing-associated decline which results in vulnerability to minor changes in health status (2,4). Frail individuals who face stressors recover slower than non-frail peers, and under some circumstances, previous homeostatic levels may not be achieved due to incomplete recovery (3). After the introduction of frailty in the 1980s (223), many definitions of frailty have been introduced (224).

2.6.1 THE PHENOTYPE AND CUMULATIVE DEFICIT MODELS

Frailty was defined as a clinical syndrome that comprised of five criteria: unintentional weight loss, self-reported exhaustion, weakness, slowness and low physical activity (Table 4). When a critical threshold of three or more of these criteria was present, the person was considered frail and those with one or two criteria were defined as pre-frail. Frailty has been suggested to overlap in part with burden from other chronic diseases (defined as 2 or more), i.e. comorbidity, and disability in activities of daily living (ADL) (defined as disability in 1 or more ADLs).

In the Cardiovascular Health Study, two prospective cohorts including 5,317 men and women aged 65 years and older were first evaluated at baseline and then followed up annually for a maximal period of 7 years. Those with Parkinson's disease, stroke, Mini-Mental scores of less than 18 and those using certain medications were excluded. At baseline, 7 % of the cohort was considered frail and 3 to 4-year frailty incidences ranged from 7 to 11 %. Those who fulfilled at least one criterion but not as many as three or more were considered pre-frail (47 % at baseline) and those who fulfilled none were considered not to be frail (46 % at baseline). (2)

Associations between baseline frailty classification and incident adverse health outcomes were assessed: frail individuals had significantly greater mortality rates at the 3-year (18 and 3 %) and 7-year (43 and 12 %) follow-ups compared to individuals who were not frail. Associations between frailty and incident hospitalization, falls and worsening disability were also observed after adjustment for covariates (including age, gender, indicator for minority cohort, income, smoking status, brachial and tibial blood pressure, fasting glucose, albumin, creatinine, carotid stenosis, history of congestive heart failure, cognitive function, major electrocardiograph abnormality, use of diuretics, promlem with IADLs, self-report health measures and a modified depression measure), showing a step-wise increase with increasing frailty status. (2)

Table 4. *Frailty phenotype[a] model criteria and measures*

Criterion	Measure
Weight loss	Self-reported unintentional weight loss of 4.5 kg or greater or 5% of body weight per year
Exhaustion	Self-reported exhaustion on three days or more per week using the US Centre for Epidemiological Studies depression scale[b]
Weakness	Grip strength, sex- and BMI-stratified; lowest quintile (20 %)
Slowness	Walking speed on a 4.57 m distance, sex- and height-stratified; lowest quintile (20 %)
Physical activity	Energy expenditures of <383 Kcal (men) and <270 Kcal (women) calculated from a LTPA questionnaire[c]

Note. [a](2), [b](225), [c](226).

The cumulative deficit model identifies frailty as the proportion of accumulated deficits, which can be symptoms, signs, functional impairments and laboratory abnormalities. Based on these deficits an index score can be calculated, representing the number of deficits proportional to the total number of deficits in the model. For example, out of 48 deficits, those scoring 12 deficits would have a frailty index score of 0.25. All deficits are weighed equally, and a minimum of 30 deficits should be included for the model to be valid. (227,228)

2.6.2 PREVALENCE OF FRAILTY

Evidence indicates that the mean prevalence of frailty among community-dwelling individuals aged 65 years and older varies greatly, from 4.0 to 59.1 %, with a weighted mean prevalence of 10.7 % according to different methods of defining frailty (229). In nursing home settings, even greater variability has been observed, with prevalence estimates ranging from 19.0 to 75.6 % (230). Much of this variance can be attributed to differences in chronological age. Among 65 to 69 year-olds, an estimated 5 % of individuals were classified as frail as opposed to those aged 85 years and older, where estimates ranged from 20 % upwards to 50 % (229).

Besides age, gender and the used frailty definition may give slightly different prevalence estimates. In a systematic review, use of either the frailty phenotype or cumulative deficit models resulted in weighted prevalence estimates of 9.9 % (95 % CI 9.6-10.2; 15 studies and 44,894 participants) and 13.6 % (95 % CI 13.2-14.0; 8 studies and 24,072 participants), respectively (229). The prevalence of frailty was higher among women (9.6 %) than men (5.2 %) irrespective of the used frailty definition (229).

2.6.3 FRAILTY AND ADVERSE HEALTH OUTCOMES

Evidence from meta-analyses of observational studies on the association between frailty and adverse health outcomes is presented in Table 5. Studies suggest that frailty has a moderate to substantial association with later risk of falls, fractures, hospitalization, dementia, nursing home admission, disability and mortality (5–10,231,232). The association between mortality and frailty has further been replicated in recent meta-analyses to include several other frailty definitions (233,234).

Table 5. *Frailty and adverse health outcomes, evidence from meta-analyses of observational studies.*

Outcome	N	OR/HR	Frail vs. non-frail	Pre-frail vs. non-frail
Falls[a]	68,723	OR	1.84 (1.43-2.38)	1.25 (1.01-1.53)
Fractures[b]	96,564	OR	1.70 (1.34-2.15)	1.32 (1.18-1.46)
Hospitalization[c]	74,900	OR	1.90 (1.74-2.07)	1.13 (1.04-1.24)
Dementia[d]	10,680	HR	1.33 (1.07-1.67)	
Nursing home admission[e]	3,528	OR	5.58 (2.94-10.60)	3.26 (1.21-8.78)
Develop/worsen ADL disability[f]		OR	2.76 (2.23-3.44)	
Develop/worsen IADL disability[f]		OR	3.62 (2.32-5.64)	
Premature mortality[g]	35,538	HR	2.00 (1.73-2.32)	1.33 (1.26-1.42)

Note. ADL=activities of daily living, IADL=instrumental activities in daily living, OR=odds ratio, HR=hazard ratio. [a](10), [b](9), [c](8), [d](231), [e](6), [f](7), [g](5).

2.6.4 PREDICTORS OF FRAILTY

Multiple frailty determinants have been identified across several areas and stages of life. Frail individuals are more commonly older, female, obese, and report difficulties with their personal finances as well as decreased health and cognition, shown in Table 6.

Early life predictors of frailty have been less studied. In a study that included five cities in Latin America, poor childhood economic situation, health and experiences of hunger were found to be associated with frailty in individuals aged 60 years and older (235). In another study, despite being associated with frailty in some analyses, childhood living conditions were not associated with frailty after adjusting for covariates (including age, gender, marital status, cigarette smoking and alcohol consumption) (236). In the Lothnian Birth Cohort, lower intelligence at 11 years of age and a lower childhood socioeconomic status (SES) were associated with frailty decades later, whereas childhood home environmental deprivation was not (237).

Table 6. *Factors associated with frailty across the life-course*

Socio-demographic
Older age[1,2,3,4]
Female gender[1,3,4]
Lower income[1,2,3,5], lower educational level[1,2,3,5]
Physical
Obesity (BMI≥30)[2,3,5]
Higher number of ADL problems[4]
Reduced extremity function[4]
Biological
Individual chronic diseases[1,2,3], total number of chronic diseases[1,2]
Polypharmacy[11]
High C-reactive protein[5,7,8], Elevated markers of blood clotting[9]
Low level of active vitamin D[5]
Insulin resistance[8]
Lifestyle-related
Smoking[2,4,5]
Alcohol consumption (no/past drinker)[2], (no/high consumption)[12]
Low adherence to a Mediterranean-style diet[6,10]
Psychological
Poor self-rated health[1,3]

Poor cognitive function[1,4,5]
Depressive symptoms[2,5]

Note. [1](2), [2](12), [3](238), [4] (13), [5](239), [6](240), [7](241), [8](242), [9](243), [10](244), [11](14), [12](245)

2.6.5 MECHANISMS IN FRAILTY

Inflammation is a key host defence mechanism against microbial invasion, but purposeless activation of the innate immune signaling and related mechanisms may lead to prolonged inflammation without microbes, and again, increased circulating levels of proinflammatory cytokines including interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and interferon gamma (INF-ɣ) and proteins as C-reactive protein (CRP) (246,247). Levels of these circulating cytokines may be further exacerbated by oxidative stress, accumulation of advanced glycation end-products, mitochondrial dysfunction, proinflammatory lipid signaling, cell senescence and epigenetic mechanisms (248).

Increased levels of inflammatory cytokines may have harmful effects on tissues and organs that lie on the pathway to frailty. In muscle tissue, increased levels of proinflammatory cytokines (Il-1, IL-6 and TNF- α) may reduce the viability of the tissue through 1) reduced IGF-mediated metabolism, 2) dysfunction of blood vessels and blood supply and 3) through impairing the regenerative effects of satellite cells on muscle tissue (249). Sarcopenia, which refers to ageing-related loss of skeletal muscle mass, lies on the central pathway to frailty (250,251).

It has been suggested that frailty would share similar pathology to delirium and cognitive decline (3). The presence of an inflammatory trigger may result in the activation of proinflammatory cytokines and inflammatory mediators in the central nervous system, that would trough neural or humoral mechanisms, trigger activation of microglial cells, which are resident macrophages of the central nervous system. Another mechanism involves the production of reactive oxygen and nitrogen species, which in turn, may enhance inflammatory responses. (252)

The endocrine mechanisms predisposing to frailty may involve dysregulations in cortisol, growth hormone and androgen metabolism. Dysregulation and abnormal sensitivity to inflammatory stimuli in the HPA-axis may lead to chronically elevated cortisol levels and muscle atrophy. Decreased secretion of growth hormone and production of IGFs may alter body composition by increasing the proportion of fat and decreasing the proportion of lean mass. Moreover, lower circulating levels of testosterone and vitamin D have been reported among frail individuals. (253)

2.6.6 PREVENTION OF FRAILTY

Randomized controlled trials (RCTs) aimed at reducing frailty have included interventions that involved physical activity, nutritional counselling and memory training. In studies where physical activity interventions with durations ranging from 3 to 12 months were used, reductions in the mean numbers of respective frailty criteria (254–256) as well as frailty prevalence (257) have been observed. Similarly, in studies where combined physical activity and nutritional interventions were used, decreases in the prevalence of frailty (258–260) and its criteria (261) were observed. In a study where nutritional, cognitive and physical interventions were applied, combination interventions resulted in the greatest reductions in mean frailty scores compared to the control group (262).

3 AIMS OF THE STUDY

The aim of this study was to explore frailty from a life-course perspective by investigating associations between factors taking place during gestation, childhood, adulthood and old age and frailty.

The specific aims of the study were as follows:

1. To explore the association of maternal BMI, birth order or their new borns and body sizes at birth, childhood socioeconomic status, and frailty in old age (I).

2. To determine the relationship between infant and childhood growth and susceptibility to frailty in old age (II).

3. To study the association between wartime separation from both parents, a severe form of ELS, and frailty in old age (III).

4. To explore prospective associations between LTL at 61y and frailty at 71y, cross-sectional associations between LTL and frailty at 71y and the association between telomere shortening across 10 years of follow-up and frailty (IV).

4 SUBJECTS AND METHODS

4.1 HELSINKI BIRTH COHORT STUDY

Helsinki Birth Cohort Study is a longitudinal birth cohort that includes more than 20,000 individuals born in Helsinki between the years 1924-1933 and 1934-1944. The younger cohort consists of 13,345 individuals who were born either in Helsinki University Central Hospital (HUCH) or Helsinki City Maternity Hospital, between 1934 and 1944. This thesis focuses on the 8,760 participants, 4,630 men and 4,130 women, who were born in HUCH.

All participants visited child welfare clinics in the city of Helsinki where a majority also went to school. The assignment of a unique personal identification number to all Finnish residents in 1971 enabled tracing of the study participants and their inclusion in the study. In the year 2000, 7,079 individuals born in HUCH were traced and sent a questionnaire which was modified from those used previously in the Health 2000 and FINRISK studies (263). The questionnaire, which was filled in by 4,595 participants, included questions on e.g. the respondents' overall health status, use of medication, lifestyle and socioeconomic circumstances.

Of the 4,595 individuals who completed the questionnaire, a sample of 2,902 individuals was drawn using random number tables and was invited to take part in a clinical study. 2,003 cohort members participated in the baseline clinical examination which took place between 2001 and 2004. Of the 2,003 individuals who were examined clinically, 151 had died, 212 had declined further participation in the study and 236 lived further than within a 100-kilometer distance from Helsinki at the time of the follow-up clinical examination between 2011 and 2013. As a result, 1,404 participants were invited and of which 1,094 participated in the follow-up clinical examination. These 1,094 participants formed the analytical sample of the present study, illustrated in Figure 3.

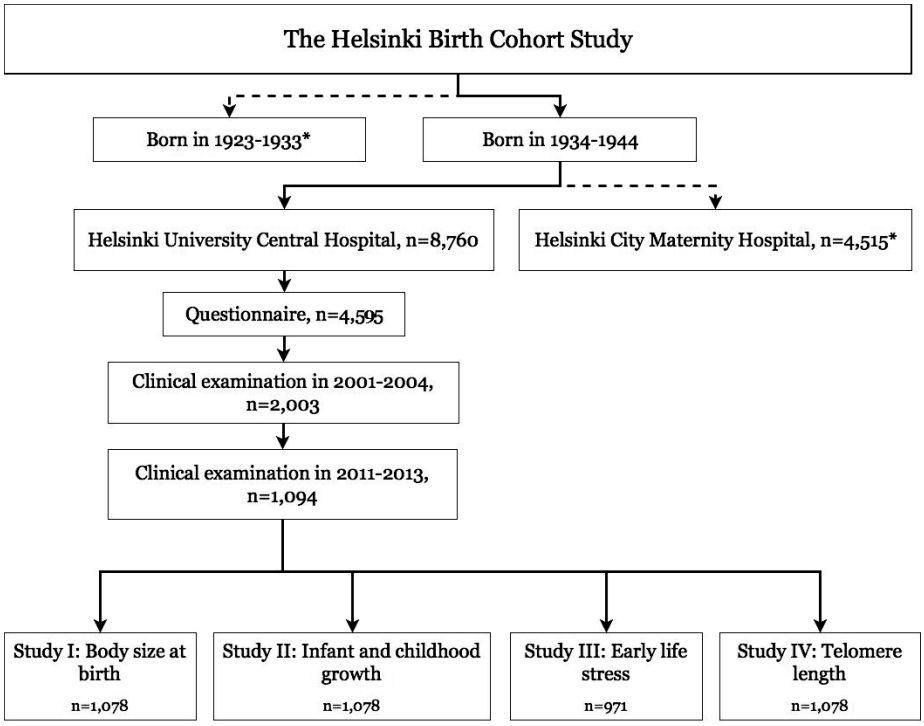

Figure 3 Flow chart representing the distribution of participants included in the present sub-study of the Helsinki Birth Cohort Study.

4.2 EARLY LIFE CHARACTERISTICS

4.2.1 MEASUREMENTS AT BIRTH

Data on maternal weight, height, last menstrual period and parity had been recorded upon admission to hospital in labor and were later extracted from hospital birth records, which had been stored in the Helsinki City archives. Information of their newly born babies, extracted from hospital birth records, included measurements of birth weight and birth length. BMI at birth was calculated as weight in kilograms divided by square of length in meters (kg/m^2).

4.2.2 MEASUREMENTS IN INFANCY AND CHILDHOOD

Records held at child welfare clinics and school healthcare facilities provided information on the serial measurements of the participants' weight and height in infancy and childhood. On average, 17 measurements of size including height and weight were available for each participant from birth to 11 years of age. Besides measurements of size, information on childhood SES was

extracted from these records, which had been stored in the Helsinki City archives. Childhood SES was determined using information on the father's highest occupation and classified as manual workers, lower middle class and upper middle class according to the classification system by Statistics Finland (264).

4.2.3 WARTIME SEPARATION FROM BOTH PARENTS

Approximately 70,000 Finnish children from various backgrounds were evacuated abroad unaccompanied by their parents during WWII. The children were sent to foster care primarily to Sweden, but also to Denmark, through Government-aided programs and personal relations. While factors as shelter from bombardments and food shortages may have influenced participation in these voluntary evacuations, the effects of various political and family-related factors cannot be excluded (125,265).

The evacuated children were separated from their new foster families and sent back to their original families after the war was over. Because Finland fought two wars during WWII, some children may have experienced separation from their original families more than once.

Registers held at the Finnish National Archives provide documentation of the 48,628 children who were sent abroad through the Finnish Government. Information on the age at and duration of the separation was extracted from these registers. To identify the children who had been evacuated through personal relations and thus were not included in the registers held by the Government, self-reported information on wartime evacuations was gathered using questionnaires at the baseline clinical examination between the years 2001 and 2004.

The present study included 117 (12.0 %) war evacuees. Register information on duration of and age at evacuation was available for 99 and 101 participants, respectively. The age at evacuation was categorized into two groups (under the age of 4 or 4 years and older) based on the cohort median, which was 3.62 years. The duration of the separation was divided into three groups (under 1 year, from 1 year to 2 years, more than 2 years) in accordance with previous publications (141,266). Self-reported evacuation data were available for 16 participants. Of the original cohort of 1,078, separation status was missing for 106 participants, resulting in a sample of 972 individuals with data on both wartime separation status and frailty.

4.3 CHARACTERISTICS IN ADULTHOOD AND OLD AGE

4.3.1 BASELINE CLINICAL EXAMINATION

The baseline clinical examination included 2,003 individuals and was carried out in 2001-2004. The participants had fasted overnight before attending the

examination. Written informed consent was obtained from each participant prior to the measurements carried out by trained study nurses.

Anthropometric measurements including weight in light indoor clothing without shoes rounded to the nearest 0.1 kg and height rounded to the nearest 0.1 cm were measured together with an estimate of body composition. Waist circumference was measured at midpoint between the iliac crest and the lowest rib. Body fat percentage was assessed using the InBody 3.0 eight-polar tactile electrode system (Biospace Co. Ltd, Seoul, Korea). Segmental multifrequency analyses (5, 50, 250 and 500 kHz) were performed for trunk and each limb. The method has been found to give accurate estimates of body composition (267,268).

Standard laboratory testing including assessment of fasting plasma glucose, blood lipoproteins, markers of inflammation and adipocytokines was performed. Furthermore, each participant underwent a 2-hour 75 g oral glucose tolerance test. Blood pressure was measured in a sitting position as the mean of two consecutive measurements from the right arm using a standard sphygmomanometer.

Self-administered questionnaires provided information on chronic physician-diagnosed diseases (e.g. hypertension, CVD and type 2 diabetes) and lifestyle-related behaviors including smoking habits (coded as current smoker [1 ≤ cigarettes per day], former smoker, never smoked) and physical activity (coded as sedentary, brisk walking or comparable activity 2 times a week at most or 3 or more times per week).

Adult SES was defined using information on occupational status from Statistics Finland. Information on maximal occupational status attained at 5-year intervals between the years 1970 and 2000 was used to group the participants into manual workers, self-employed, lower middle class and upper middle class.

4.3.2 FRAILTY

Frailty was assessed at the follow-up clinical examination between the years 2011 and 2013 using the phenotype definition put forward by Fried (2). This validated method for assessing frailty consists of five criteria that include weight loss, exhaustion, low physical activity, slowness and weakness.

Weight loss was assessed using a question from the Beck Depression Inventory (BDI) (269), and those who reported losing 5 kg or more recently, met the criterion. The following question was used to evaluate weakness: “How many times during the last week have you felt unusually tired or weak?” The criterion was met if the response was “On three days or more”. The validated Kuopio Ischemic Heart Disease Risk Study (KIHD) questionnaire (270) was used to assess LTPA. The criterion of low physical activity was met if the participant’s total LTPA time (including e.g. walking, resistance training and gardening) was 1 hour or less per week. In case of missing KIHD LTPA data, as was the case with 42 individuals, low physical activity was evaluated using

the following question: “In total, how many hours per week do you do the following sports (including e.g. walking, jogging, cycling, swimming, gymnastics and group exercise)?” Those who reported their total duration of physical activity as 1 hour per week at most met the criterion.

Objective measurements of walking speed and grip strength were used to assess the criteria of slowness and weakness, respectively. The criterion of slowness was evaluated by measuring maximal walking speed over a 4.57-meter distance. Sex-specific cut-offs for medium height (for men ≤175.9 cm cut-off was 1.65 m/sec and >175.9 cm 1.83 m/sec and for women ≤162.2 cm cut-off was 1.47 m/sec and >162.2 cm 1.55 m/sec) were used to identify the slowest 20 % that met the criterion. For weakness, grip strength of the dominant hand was measured using an adjustable dynamometer chair (Good Strength, Metitur Ltd, Jyväskylä, Finland), and for the assessment of the criterion, sex-specific quartiles of BMI were used to identify the 20 % with the lowest grip strength score.

The participants were classified as either frail (those fulfilling three or more criteria), pre-frail (those fulfilling one or two criteria) or non-frail (those fulfilling no criteria).

4.3.3 LEUKOCYTE TELOMERE LENGTH

LTL was measured at the baseline clinical examination in 2001-2004 and at the follow-up clinical examination after a 10-year period between 2011 and 2013. Commercially available kits (QIAamp blood Maxi kit and DNeasy blood and tissue kit, Qiagen s.r.l. [Venlo, The Netherlands]) were used according to the manufacturer’s instruction to extract DNA from peripheral whole blood. DNA contamination for salts and other contaminants was assessed by comparing ultraviolet absorbance at wavelengths of 260 nm to absorbance at 230 nm (260/230 ratio) and to 280 nm (260/280 ratio), respectively. Samples with ratios ranging between 1.7 and 2.1 were considered pure and could hence be studied further. DNA integrity was assessed by electrophoresis in 0.8 % agarose/0.5x TBE with 0.1 µl/ml ethidium bromide at ~100 V for 15 to 25 minutes.

Using slightly different methodology, a real time quantitative PCR approach was applied at both time points to measure relative LTL. First in 2001-2004, LTL was determined as the ratio of telomere DNA to hemoglobin beta single-copy gene signal intensities, as described previously (160,271). In brief, based on the method described by O’Callaghan (272), reaction-specific standard curves were created by including a synthetic oligomer Sigma (St Louis, Missouri, USA) dilution series, hbg-120-mer and tel14x in each plate. Furthermore, a constant 10 ng of total DNA per reaction was maintained by adding plasmid DNA (pcDNA3.1) to each standard. Quality control was carried out using the Bio-Rad CFX Manager software v.1.6 9 (Bio-Rad Laboratories, Hercules, CA, USA). Four genomic DNA control samples were included in all plates for calibration of the plate effect and further, to monitor the coefficient

of variation (CV), which was 21.0 % for the telomere reaction, 6.0 % for the β-hemoglobin reaction, and 24.8 % for their ratio (T/S). Telomere and reference gene signals were normalized to the corresponding mean of four control samples that were analyzed for each qPCR plate before taking the T/S ratio to account for the plate effect.

Later in 2011-2013, LTL was measured using a multiplex quantitative real-time PCR method, described previously by Cawthon and with minimum modifications (161). In brief, a standardized DNA concentration of 4 ng/μl was combined with telomere primers pair 900 nM, beta globin (as single-copy gene) primers pair 500 nM, and 2X master mix (IQ Sybr green supermix, Bio-Rad Laboratories). PCR reactions using the original thermal cycle (161) set up in a 384-well plate (CFX384 Touch Real-Time PCR detection system, Bio-Rad Laboratories) were carried out in a final volume of 10 μl. A 1:3 serial dilution curve was run for assessment of the efficiency of the amplification. A dedicated software (CFX Manager Software, Bio-Rad Laboratories) was used to analyse threshold cycles for both beta-globin and telomere amplification. The ratio between the amplification of the telomere sequence (T) and that of a single copy gene (S), expressed as a relative telomere length (T/S), was measured for each sample in the same well and PCR run, and additionally, normalized by the use of a common reference DNA sample. Samples were run in triplicate; the mean coefficient of variation of each triplicate was 6.0%, and the mean inter-assay CV% was 6.2%.

Information on LTL was available for 1,042 and 1,061 participants, respectively at the baseline and follow-up clinical examinations. 1,037 individuals had their measurements taken on both time points. Telomere shortening during the 10-year period was calculated adjusting for the baseline relative LTL measurement (relative change in LTL = {[LTL at 71] – [LTL at 61]} / [LTL at 61] × 100) to avoid error due to different methodology used.

4.4 STATISTICAL METHODS

The baseline characteristics from studies I-IV were expressed as means and standard deviations (SD) in case of continuous and as proportions for dichotomous or categorical variables. Differences between groups were assessed using Students t-test or one-way ANOVA and Pearson's chi-squared test, respectively for normally distributed continuous and categorical values. Interaction terms were created to test whether associations between predictor and outcome variables were depended on other predictor variables. If a statistically significant ($p<0.05$) sex x predictor interaction on the outcome was observed, the analyses were presented separately for men and women.

In study I, multinomial regression analyses were used to study associations between early life determinants (including birth weight, birth length, birth BMI, parity and mother's BMI) and frailty in old age. Furthermore, the associations between childhood and adult SES and frailty were studied. While

no interactions between sex and early determinants on frailty were observed, the results were pooled by sex. The models were first adjusted for sex and age. Further adjustments were made for covariates including gestational age, childhood and adulthood SES, BMI in adulthood, smoking, hypertension and diabetes. Because of missing covariate data (maximum proportion of data missing was 3.1 %), multiple imputations were used to obtain a complete dataset. Altogether 20 imputed datasets were generated using information from all variables that were included in the analyses. The analyses were first performed using complete data available for all main variables and covariates and then using the imputed datasets combining the effect estimates using Rubin's rules. While these results were very similar, findings on imputed data were presented.

In study II, associations between serial measurements of growth and frailty were studied using multinomial regression analyses. To achieve this, measurements of size for each individual, ranging from birth to 11 years of age, were converted into z scores that represent the difference from the cohort mean and are expressed as standard deviations (273). By using previous growth measurements as a predictor of future size, differences between predicted and measured size at each age were examined using the residuals from linear regression, referred to as conditional growth. Conditional growth was calculated for the age periods of 0-6 months, 6-24 months and 2-11 years. Conditional BMI gain was analysed separately for men and women because of an interaction between sex and conditional BMI gain for 2-11 years on frailty. The analyses were first adjusted for age and sex without the exception of conditional BMI gain where analyses were performed separately for men and women. The analyses were then adjusted further for childhood and adult SES, BMI in adulthood, smoking, hypertension and diabetes.

Additionally, in study II, associations between individual measurements of size including height, weight and BMI and frailty were examined. The associations between weight, height and BMI measured at birth and at 1, 2, 7 and 11 years of age and frailty were studied using multinomial regression analyses. The combined associations of size at birth and that measured at 11 years and frailty were assessed by first dividing the participants into three groups according to their birth weight and BMI at 11 years and second, by observing differences in the prevalence of frailty between the groups. Age at BMI rebound, a point in time at which body fatness normally decreases to minimum before increasing into adolescence (94), was estimated by calculating age at minimum BMI between the ages from 1 to 12 years. The models were first adjusted for age and sex, and additionally for covariates as listed previously for study II, since no interactions between sex and the covariates on frailty were observed.

In study III, a multinomial regression analysis was conducted to study associations between wartime separation (indicating ELS) and frailty. Additional binomial logistic regression analyses were performed to assess associations between wartime separation and frailty criteria. Although no

interactions between sex and wartime separation status on frailty were observed, the analyses were performed separately for men and women due to previous findings on sex differences in the association between ELS and later health outcomes (266). The results were first adjusted for age and then additionally for covariates including birth weight, childhood and adult SES, smoking, hypertension and diabetes. As in study I, a complete dataset on covariates was acquired by multiple imputation (maximum proportion of data missing was 1.1 %), and while the results were very similar, findings are presented based on imputed data.

In study IV, the association of LTL and the rate of telomere shortening during a 10-year period and frailty were studied using multinomial regression analyses. No significant interactions between sex and telomere length on frailty were observed. The analyses were first adjusted for age and sex, and furthermore for adult SES, adult body fat percentage, smoking and the presence of CVD and diabetes.

In studies I-IV, additional binomial regression analyses were performed to determine whether any of the individual frailty criteria were driving the association between early life predictor variables and frailty. Without the exception of study IV where significant ($p<0.05$) interactions between sex and telomere measurements on *slowness* were observed, the results were reported pooled by sex. All analyses were performed two-tailed, the level of significance was set at $p<0.05$. Analyses were carried out using SPSS (IBM SPSS Statistics for Windows, Version 23.0 IBM Corp. Released 2015, Armonk, NY).

4.5 ETHICAL CONSIDERATIONS

The present study complies with the guidelines of the Declaration of Helsinki. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa and the ethical committee at the National Public Health Institute have approved of the clinical study protocol. Written informed consent was obtained from each participant before initiating any study procedures.

5 RESULTS

Characteristics of the 1,078 individuals, 475 men and 603 women, are summarized in Table 7. While the majority of the participants came from a background of manual workers, upward social mobility was observed particularly among women, who later in their adult lives were most often classified as representatives of the lower middle class. At the time of the baseline clinical examination between the years 2001-2004, men were more often current smokers and had diabetes (p-values ≤0.042) than women.

Frailty, which was assessed at the time of the follow-up clinical examination in 2011-2013, was more prevalent among women (4.3%) than men (2.7%) at the average ages of 71.1 (SD 2.6) and 70.8 years (SD 2.8), respectively. Although no significant sex difference in frailty was found, the criteria of exhaustion (9.6% and 5.1%) and low physical activity (11.6% and 7.4%) were more commonly met among women than men (p-values ≤0.020).

Table 7 *Characteristics of the study population.*

	Whole cohort		Men		Women		
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**p[a]**
Childhood SES	1074						0.072
Upper middle class (%)		19.5		22.3		17.2	
Lower middle class (%)		41.9		22.7		22.2	
Manual workers (%)		58.1		54.7		60.4	
Adult SES	1078						<0.001
Upper middle class (%)		16.8		23.6		11.4	
Lower middle class (%)		46.0		28.0		60.2	
Self-employed (%)		8.5		9.3		8.0	
Manual workers (%)		28.7		39.2		20.4	
Characteristics in late adulthood (mean age 61 years)							
BMI (kg/m²)	1066	27.0 (4.5)	468	26.8 (3.8)	598	27.3 (5.0)	0.439
Body fat (%)	1039	28.7 (8.0)	454	22.9 (5.5)	585	33.2 (6.6)	<0.001
Current smoker (%)	1071	19.1	471	20.8	600	17.8	<0.001
Hypertension (%)[b]	1075	31.8	473	32.1	602	31.6	0.841
Cardiovascular disease (%)[b]	1075	5.6	473	4.7	602	6.3	0.239
Diabetes (%)[b]	1075	5.2	473	6.8	602	4.0	0.042
Characteristics in old age (mean age 71 years)							
Frailty classification	1078						0.383
Non-frail (%)		56.4		56.6		56.2	
Pre-frail (%)		40.0		40.6		39.5	

Frail (%)	39	3.6	13	2.7	26	4.3	
Frailty criteria							
Weight loss (%)		5.7		6.5		5.1	0.361
Exhaustion (%)		7.6		5.1		9.6	0.005
Low physical activity (%)		9.7		7.4		11.6	0.020
Slowness (%)		19.8		20.2		19.9	0.910
Weakness (%)		19.9		19.7		20.1	0.858

Note. SD=standard deviation, SES=socioeconomic status, BMI=body mass index. [a] Difference between men and women. [b] Self-reported.

A graded increase in the prevalence of comorbidities including reported CVD, diabetes and hypertension was observed among the non-frail, pre-frail and frail participants, illustrated in Figure 4. Furthermore, the percentage of individuals with a manual working family background (p^{trend}=0.118) as well as the percentage of individuals who were classified as manual workers in adulthood (p^{trend}=0.001) increased at the expense of other socioeconomic groups with progressing frailty classification (Figure 5). Similarly, those who were classified as frail at the mean age of 71 years, had had greater BMI and had more often been smokers at the average age of 61 years (p-values ≤0.006).

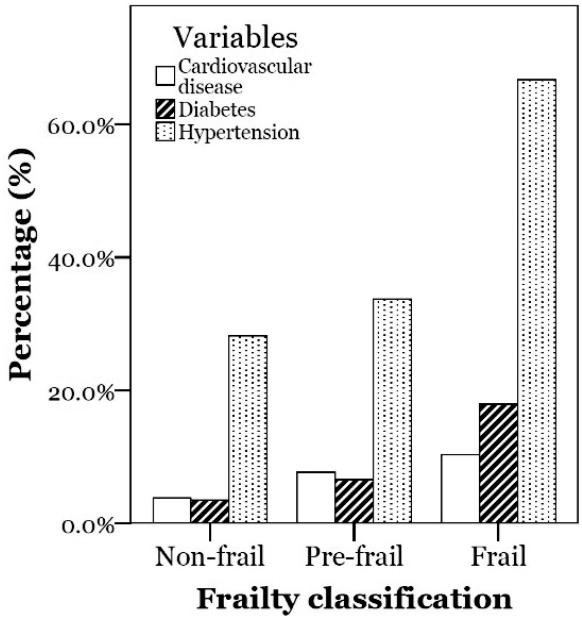

Figure 4 Percentage distributions of cardiovascular disease, diabetes and hypertension among non-frail, pre-frail and frail cohort members.

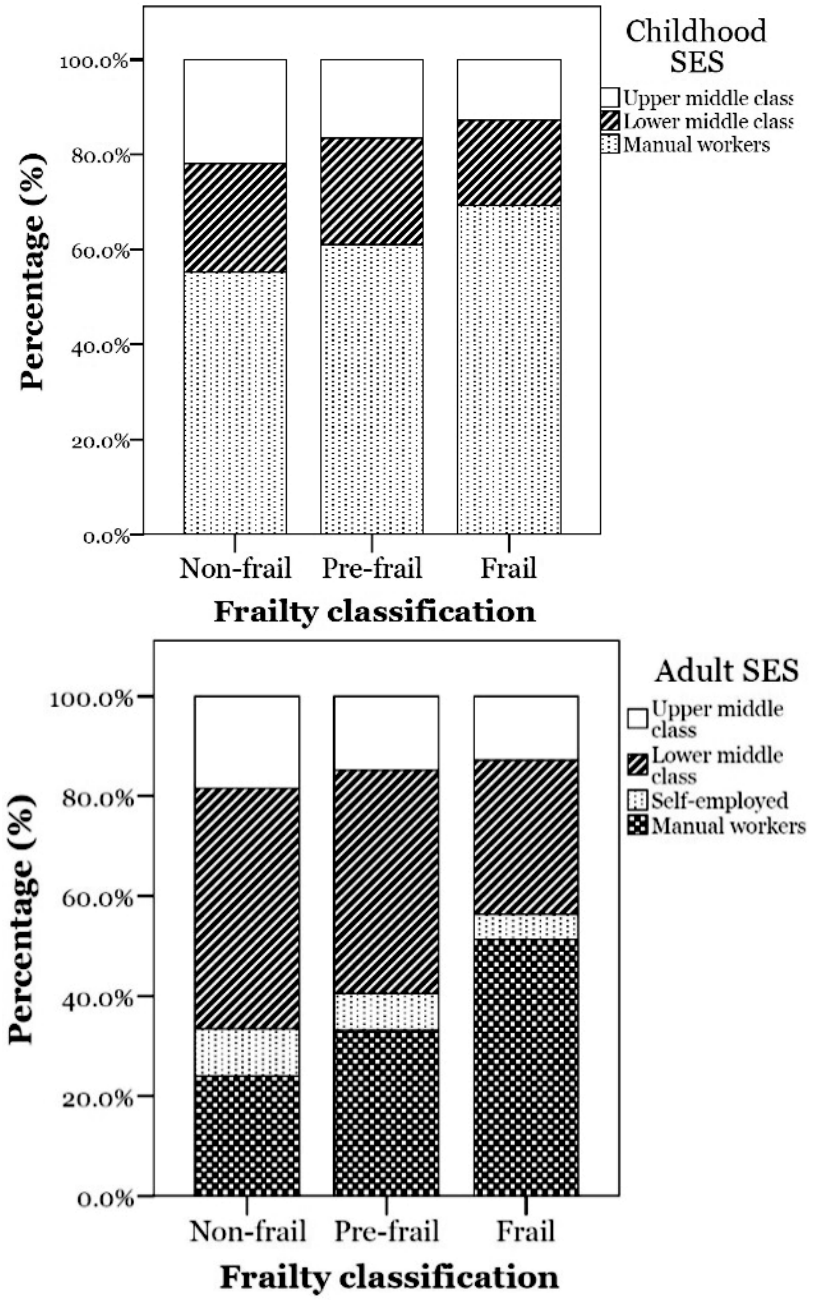

Figure 5 Percentage distribution of childhood and adult SES among non-frail, pre-frail and frail cohort members.

5.1 BODY SIZE AT BIRTH, PARITY, MATERNAL BMI AND FRAILTY

The newborn weighed on average 3.42 kg (SD 0.46) and were 50.4 cm (SD 1.9) long, with the baby boys being slightly bigger at birth than their female counterparts (p-values <0.001, Table 8). Their mothers, who carried the babies for a mean duration of 39.4 weeks (SD 1.8), had an average BMI of 26.5 kg/m^2 (SD 2.8) before admission on labour. Primipara women, who constituted 45.9% of the participants' mothers, gave birth to boys slightly more often than girls, and reversely, to girls more often than boys if the mother had previously been admitted to labour (p^{trend}=0.012).

Table 8 *Early life characteristics of the participants.*

	Whole cohort		Men		Women		p[a]
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Birth characteristics							
Birth weight (kg)	1078	3.42 (0.46)	475	3.48 (0.49)	603	3.36 (0.44)	<0.001
Birth length (cm)	1066	50.4 (1.9)	469	50.7 (2.0)	597	50.1 (1.8)	<0.001
Birth BMI (kg/m^2)	1066	13.4 (1.2)	469	13.5 (1.3)	597	13.4 (1.2)	0.145
Gestational age (weeks)	1045	39.4 (1.8)	464	39.3 (1.8)	581	39.4 (1.8)	0.301
Mother's BMI (kg/m^2)	935	26.5 (2.8)	410	26.6 (2.9)	525	26.5 (2.8)	0.228
Parity	1078						0.012
First born (%)		45.9		46.1		45.8	
Second born or later (%)		54.1		53.9		54.2	

Note. SD=standard deviation, BMI=body mass index. [a] Difference between men and women.

An inverse association was observed between different measures of body size at birth and frailty, shown in Table 9. The relative risk ratio (RRR) of frailty compared to non-frail individuals was decreased by 60% per each 1 kg increase in birth weight (RRR 0.40, 95% CI 0.19, 0.82, p=0.012), adjusted for age and sex. A similar association was observed for each 1 cm increase in birth length (RRR 0.78, 95% CI 0.66, 0.91, p=0.002). A one unit increase in birth BMI, in which the effects of birth weight and length are combined, corresponded to a significantly decreased RRR of frailty (RRR 0.03, 95% CI 0.003, 0.25, p=0.002) compared to the non-frail, in analyses adjusted for age and sex. All associations persisted after further adjustment for gestational age, childhood and adult SES, adult BMI, smoking behaviour, hypertension and diabetes. The RRR's of frailty were 0.36 (95% CI 0.15, 0.85, p=0.020), 0.78 (95% CI 0.64, 0.95, p=0.012) and 0.02 (95% CI 0.001, 0.73, p=0.033), respectively for one-unit increase in birth weight, length and BMI in the fully adjusted analyses. No associations between birth order and maternal BMI and frailty in old age were observed.

Table 9 *Relative risk ratios of frailty and pre-frailty per one-unit increase (kg, cm, or kg/m^2) in early life characteristics compared to the non-frail individuals for men and women combined.*

	Model 1[a]		Model 2[b]		Model 3[c]	
	RRR (95% CI)	**p**	**RRR (95% CI)**	**p**	**RRR (95% CI)**	**p**
Birth weight						
Non-frail	ref.		ref.		ref.	
Pre-frail	0.73 (0.56, 0.96)	0.023	0.77 (0.57, 1.04)	0.093	0.73 (0.53, 0.99)	0.044
Frail	0.40 (0.19, 0.82)	0.012	0.36 (0.16, 0.80)	0.012	0.36 (0.15, 0.85)	0.020
Birth length						
Non-frail	ref.		ref.		ref.	
Pre-frail	0.92 (0.86, 0.98)	0.014	0.93 (0.86, 1.00)	0.049	0.92 (0.85, 0.99)	0.031
Frail	0.78 (0.66, 0.91)	0.002	0.76 (0.63, 0.91)	0.003	0.78 (0.64, 0.95)	0.012
Birth BMI[d]						
Non-frail	ref.		ref.		ref.	
Pre-frail	0.43 (0.08, 2.28)	0.322	0.55 (0.10, 3.00)	0.488	0.52 (0.08, 3.25)	0.519
Frail	0.03 (0.003, 0.25)	0.002	0.03 (0.003, 0.34)	0.004	0.02 (0.001, 0.73)	0.033
Birth order[e]						
Non-frail	ref.		ref.		ref.	
Pre-frail	1.09 (0.85, 1.41)	0.486	1.14 (0.88, 1.47)	0.319	1.13 (0.87, 1.47)	0.350
Frail	1.59 (0.82, 3.06)	0.168	1.83 (0.94, 3.58)	0.076	1.83 (0.95, 3.53)	0.088
Mother's BMI in late pregnancy						
Non-frail	ref.		ref.		ref.	
Pre-frail	1.11 (0.85, 1.45)	0.455	0.97 (0.93, 1.02)	0.252	0.95 (0.91, 1.00)	0.062
Frail	1.04 (0.93, 1.17)	0.462	1.04 (0.98, 1.10)	0.534	0.99 (0.89, 1.11)	0.909

Note. RRR=relative risk ratio, BMI=body mass index. [a] Adjusted for sex and age. [b] Adjusted for Model 1 plus gestational age and childhood and adult SES. [c] Adjusted for Model 2 plus adult BMI, smoking, hypertension and diabetes. [d] Quadratic term included. [e] First born vs. second or later.

To asses which of the individual frailty criteria were driving the observed associations between early life determinants and frailty, additional analyses were performed focusing upon the individual criteria. Results from these analyses are shown in Table 10. Inverse associations between birth weight, birth length and birth BMI and the criteria of *exhaustion, low physical activity* and *weakness* were found.

The corresponding odds ratios (OR's) of meeting the criteria of *exhaustion* and *weakness* were decreased (age- and sex-adjusted OR's 0.60, 95% CI 0.37, 0.99; p=0.049 and 0.67, 95% CI 0.48, 0.94; p=0.020, respectively) per 1 kg increase in birth weight. The associations became non-significant after adjustment for potential mediators. Birth BMI was also associated with *exhaustion* and *weakness,* however, associations persisted after adjustment for sex, age, childhood and adult SES, adult BMI, smoking, hypertension and diabetes (adjusted OR's 0.12, 95% CI 0.02, 0.59; p=0.010 and 0.14, 95% CI 0.03, 0.71; p=0.018, respectively) for *exhaustion* and *weakness.*

In a similar fashion, a 1 cm increase in birth length was associated with a decreased OR of fulfilling the criteria of *low physical activity* and *weakness* (age- and sex-adjusted OR's 0.89, 95% CI 0.80, 0.99; p=0.026 and 0.91, 95% CI 0.84, 0.98; p=0.017, respectively). While the association between birth length and *weakness* became non-significant after additional adjustment, the association between birth length and *low physical activity* was little changed (OR 0.88, 95% CI 0.78, 0.99; p=0.030) after adjustment for potential confounders. No associations between body size at birth and the criteria of *weight loss* and *slowness* were observed.

Table 10 *Odds ratios of selected frailty criteria per one-unit increases (kg, cm, and kg/m^2) in early life characteristics.*

	Model 1[a]		Model 2[b]		Model 3[c]	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Birth weight						
Exhaustion	0.60 (0.37, 0.99)	0.049	0.67 (0.38, 1.15)	0.146	0.67 (0.38, 1.18)	0.166
Weight loss	0.97 (0.55, 1.72)	0.924	1.12 (0.59, 2.15)	0.495	1.11 (0.57, 2.15)	0.763
Low physical activity	0.83 (0.53, 1.29)	0.411	0.83 (0.51, 1.36)	0.467	0.80 (0.48, 1.32)	0.384
Slowness	0.84 (0.61, 1.17)	0.309	0.86 (0.59, 1.25)	0.431	0.84 (0.57, 1.23)	0.372
Weakness	0.67 (0.48, 0.94)	0.020	0.73 (0.51, 1.06)	0.103	0.77 (0.53, 1.12)	0.166
Birth length						
Exhaustion	0.93 (0.82, 1.04)	0.202	0.94 (0.83, 1.08)	0.388	0.95 (0.84, 1.09)	0.490
Weight loss	0.95 (0.83, 1.09)	0.475	0.99 (0.86, 1.17)	0.991	1.00 (0.86, 1.17)	0.987
Low physical activity	0.89 (0.80, 0.99)	0.026	0.88 (0.78, 0.99)	0.035	0.88 (0.78, 0.99)	0.030
Slowness	0.94 (0.87, 1.01)	0.108	0.92 (0.85, 1.01)	0.080	0.92 (0.84, 1.01)	0.080
Weakness	0.91 (0.84, 0.98)	0.017	0.92 (0.84, 1.01)	0.067	0.93 (0.85, 1.01)	0.089
Birth BMI[d]						
Exhaustion	0.08 (0.02, 0.39)	0.002	0.10 (0.02, 0.50)	0.005	0.12 (0.02, 0.59)	0.010
Weight loss	1.31 (0.07, 26.39)	0.861	1.50 (0.09, 23.98)	0.774	1.88 (0.10, 34.00)	0.670
Low physical activity	0.22 (0.04, 1.19)	0.079	0.22 (0.04, 1.30)	0.094	0.25 (0.04, 1.49)	0.127

Slowness	0.39 (0.07, 1.17)	0.081	0.40 (0.09, 1.71)	0.216	0.45 (0.10, 1.97)	0.292
Weakness	0.09 (0.02, 0.49)	0.005	0.12 (0.02, 0.65)	0.014	0.14 (0.03, 0.71)	0.018

Note. OR=odds ratio, BMI=body mass index. [a] Adjusted for sex and age. [b] Adjusted for Model 1 plus gestational age and childhood and adult SES. [c] Adjusted for Model 2 plus adult BMI, smoking, hypertension and diabetes. [d] Quadratic term included.

5.2 GROWTH IN INFANCY AND CHILDHOOD, AGE AT ADIPOSITY REBOUND AND FRAILTY

Serial measurements of weight and height of the cohort members at ages 1, 2, 7 and 11 years are shown in Table 11. Differences in size originating from birth (Table 8) in which the boys were heavier, taller and had a higher BMI than the girls, persisted into childhood but had levelled off by age 11 years. Besides associations between body size at birth and frailty (Table 9), no associations between size at 1, 2, 7 or 11 years and frailty in old age were observed. When birth weight was divided into thirds and BMI at the age of 11 years into three groups, the prevalence of frailty was higher (8.6%) than the cohort average (2.7%) among men who both belonged in the lowest third of birth weight and at the age of 11 years, to the group with the highest BMI (>17.5kg/m^2) (data not shown).

Conditional growth was calculated for the periods of 0-6 months, 6-24 months and 2-11 years (Table 12). Conditional growth was not associated with frailty apart from an association between conditional BMI gain from 2-11 years and frailty in men (RRR 2.36, 95% CI 1.21, 4.64; p=0.012), which was attenuated after additional adjustment (RRR 2.07, 95% CI 0.94, 4.56; p=0.072).

Table 11 *Serial measurements of body size (1, 2, 7 and 11 years) of the cohort members.*

	Whole cohort		Men		Women		
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**p[a]**
Size at 1 year							
Weight (kg)	1078	10.2 (1.0)	475	10.5 (1.0)	603	9.9 (1.0)	<0.001
Height (cm)	1078	75.7 (2.6)	475	76.7 (2.4)	603	75.0 (2.4)	<0.001
BMI (kg/m^2)	1078	17.7 (1.4)	475	17.9 (1.4)	603	17.5 (1.3)	<0.001
Size at 2 years							
Weight (kg)	1078	12.1 (1.1)	475	12.4 (1.1)	603	11.9 (1.1)	<0.001
Height (cm)	1078	86.2 (3.0)	475	86.8 (2.9)	603	85.6 (2.9)	<0.001
BMI (kg/m^2)	1078	16.5 (1.2)	475	16.7 (1.2)	603	16.4 (1.2)	0.001
Size at 7 years							
Weight (kg)	1038	22.4 (2.7)	461	22.7 (2.5)	577	22.3 (2.8)	0.022
Height (cm)	1038	120.6 (4.6)	461	121.1 (4.7)	577	120.1 (4.5)	0.001

BMI (kg/m²)	1038	15.5 (1.2)	461	15.5 (1.1)	577	15.5 (1.3)	0.623
Size at 11 years							
Weight (kg)	1041	34.1 (5.0)	459	33.9 (4.3)	582	34.2 (5.5)	0.354
Height (cm)	1040	141.8 (6.1)	459	141.8 (5.6)	581	141.7 (6.4)	0.798
BMI (kg/m²)	1039	16.9 (1.7)	458	16.9 (1.4)	581	17.0 (1.9)	0.199

Note. SD=standard deviation, BMI=body mass index. [a] Difference between men and women.

Table 12 *RRR's of frailty according to conditional weight, height in all participants and BMI gain by sex.*

	Non-frailty	Frailty			
		Model 1[a]		Model 2[b]	
	Ref.	RRR (95% CI)	p	RRR (95% CI)	p
Conditional weight gain					
0-6 months		0.93 (0.66, 1.33)	0.700	0.95 (0.65, 1.40)	0.795
6-24 months		0.99 (0.71, 1.38)	0.949	1.12 (0.77, 1.65)	0.552
2-11 years		1.14 (0.83, 1.58)	0.412	0.97 (0.68, 1.37)	0.859
Conditional height gain					
0-6 months		1.06 (0.76, 1.50)	0.723	1.11 (0.78, 1.58)	0.565
6-24 months		0.90 (0.64, 1.26)	0.541	0.98 (0.68, 1.41)	0.906
2-11 years		1.00 (0.71, 1.40)	0.982	0.93 (0.65, 1.32)	0.687
Conditional BMI gain[c]					
0-6 months					
Men		0.89 (0.49, 1.60)	0.694	0.88 (0.46, 1.67)	0.688
Women		0.75 (0.48, 1.16)	0.196	0.80 (0.50, 1.29)	0.360
6-24 months					
Men		0.72 (0.38, 1.36)	0.310	0.98 (0.47, 2.06)	0.963
Women		1.29 (0.84, 1.96)	0.241	1.25 (0.79, 1.98)	0.332
2-11 years					
Men		2.36 (1.21, 4.64)	0.012	2.07 (0.94, 4.56)	0.072
Women		1.03 (0.70, 1.49)	0.894	0.91 (0.60, 1.38)	0.653

Note. RRR=relative risk ratio, CI=confidence interval, BMI=body mass index. [a] Adjusted for age and sex. [b] Adjusted for Model 1 plus gestational age, childhood and adult socioeconomic status (SES), adult BMI, smoking, hypertension and diabetes. [c] Model 1 adjusted for age only.

Additional analyses for the individual frailty criteria were performed to determine the existence of associations between body size at 1, 2, 7 and 11 years and frailty that could not be detected in changes in the frailty classification. While no associations between body size and *exhaustion, weight loss, low physical activity* and *slowness* were observed, bigger size at 1, 2 and 7 years corresponded with a decreased OR of fulfilling the criterion of *weakness* at the mean age of 71 years (Table 13). No associations between conditional growth measured for the periods of 0-6 months, 6-24 months and 2-11 years and any of the criteria were observed.

Table 13 *Odds ratios of weakness according to measurements of body size (1, 2, 7 and 11 years) of the cohort members*

	Model 1[a]		Model 2[b]	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Size at 1 year				
Weight (kg)	0.83 (0.71, 0.98)	0.027	0.85 (0.71, 1.00)	0.053
Height (cm)	0.96 (0.90, 1.02)	0.169	0.96 (0.90, 1.02)	0.176
BMI (kg/m²)	0.92 (0.82, 1.03)	0.155	0.93 (0.83, 1.05)	0.243
Size at 2 years				
Weight (kg)	0.84 (0.72, 0.96)	0.014	0.85 (0.73, 0.98)	0.026
Height (cm)	0.97 (0.91, 1.02)	0.231	0.97 (0.92, 1.02)	0.223
BMI (kg/m²)	0.85 (0.75, 0.97)	0.019	0.87 (0.76, 0.99)	0.041
Size at 7 years				
Weight (kg)	0.92 (0.86, 0.98)	0.006	0.92 (0.86, 0.98)	0.009
Height (cm)	0.97 (0.93, 0.99)	0.042	0.96 (0.93, 0.99)	0.029
BMI (kg/m²)	0.96 (0.76, 0.99)	0.032	0.88 (0.76, 1.01)	0.067
Size at 11 years				
Weight (kg)	0.97 (0.94, 1.01)	0.109	0.98 (0.94, 1.01)	0.160
Height (cm)	0.98 (0.95, 1.00)	0.062	0.98 (0.95, 1.00)	0.059
BMI (kg/m²)	0.97 (0.88, 1.06)	0.477	0.98 (0.89, 1.08)	0.694

Note. OR=odds ratio, CI=confidence interval, BMI=body mass index. [a] Adjusted for age and sex. [b] Adjusted for Model 1 plus gestational age, childhood and adult socioeconomic status (SES), adult BMI, smoking, hypertension and diabetes.

5.3 EARLY LIFE STRESS AND FRAILTY

The study cohort in this sub-study consisted of 972 individuals, of whom 117 (12.0 %) had experienced wartime separation from both parents in childhood. The separated cohort members were on average heavier at birth (3.47 and 3.41 kg) and had reported a higher prevalence of hypertension in adulthood (41.9 and 30.4 %) compared to the non-separated individuals (n=855) who served as controls (p-values≤0.01). The mean age at separation was 4.2 years (SD 2.2) and, on average, the separated spent 1.6 years (SD 1.0) with their new foster families. At the mean age of 71 years, the percentage of frail individuals was 5.1 % for the separated cohort and 3.2 % for the non-separated cohort (p^{trend}=0.310). The prevalence of frailty was higher among the separated men (7.1 %) than the non-separated men (2.3 %, p=0.048). No differences in frailty criteria were observed between the separated and the non-separated cohort members in comparisons for both sexes combined and when analysed separately for men and women.

In Table 14, compared to the non-separated men, men experiencing wartime separation in childhood had an increased risk of frailty (age-adjusted RRR 3.93, 95% 1.02, 15.11; p=0.046) compared to the non-frail men, which

persisted after additional adjustments for confounders (RRR 5.18, 95% CI 1.16, 23.17; p=0.031). This was not observed among women (RRR 0.61, 95% CI 0.13, 2.94; p=0.550).

Table 14 *Relative risk ratios of frailty among the separated compared to the non-separated.*

	Model 1[a]		Model 2[b]	
	RRR (95% CI)	**p**	**RRR (95% CI)**	**p**
Non-frail	Ref.		Ref.	
Frail				
Whole cohort				
Men	3.93 (1.02, 15.11)	0.046	5.18 (1.16, 23.17)	0.031
Women	0.62 (0.13, 2.94)	0.550	0.58 (0.26, 1.31)	0.502

Note. RRR=relative risk ratio, CI=confidence interval. [a] Adjusted for age. [b] Adjusted for Model 1 plus birth weight, childhood and adult SES, adult BMI, smoking, hypertension and diabetes.

The age at and duration of the separation was studied further for the separated men. Younger age at separation (before the age of 4 years) was associated with an increased age-adjusted RRR of frailty (RRR 5.58, 95% CI 1.36, 22.93; p=0.017) compared to the non-separated men. Further adjustment for birth weight, childhood and adult SES, adult BMI, smoking, hypertension and diabetes had little effect on the association (RRR 6.96, 95% CI 1.28, 37.72; p=0.024). No data was available for those separated at an older age (at the age of 4 or older). The RRR of frailty was further increased with prolonged duration of the stay with the new foster family: compared to the non-separated men, men who spent more than 2 years abroad had an increased RRR of frailty (RRR 10.27, 95% CI 1.71, 61.68; p=0.011), which persisted after adjusting for covariates (RRR 12.87, 95% CI 1.29, 128.38; p=0.029). This was not seen for durations of 2 years or less (age-adjusted RRR 2.66, 95% CI 0.28, 25.15; p=0.392). In boys, no associations between separation status and any of the criteria of frailty were observed.

5.4 CHILDHOOD AND ADULT SOCIOECONOMIC STATUS AND FRAILTY

RRR's of frailty according to childhood and adult SES are shown in Tables 15 and 16, respectively. Individuals coming from families of manual workers had an increased RRR of pre-frailty (age- and sex-adjusted RRR 1.46, 95% CI 1.05, 2.04; p=0.025) compared to participants from upper middle class backgrounds. Further adjustments, first for adult SES and additionally for adult BMI, smoking, hypertension and diabetes, resulted in an attenuation of the association. No associations between childhood SES and frailty were observed.

In terms of adult SES, a graded increase in the risk of pre-frailty (RRR 1.82, 95% CI 1.23, 2.68; p=0.003) and frailty (age and sex adjusted RRR 3.18, 95% CI 1.15, 8.80; p=0.026) compared to non-frailty was observed among those classified as manual workers compared to those who were classified as upper middle class persons. When the comparison was performed for those classified as having a lower middle class working history relative to those with an upper middle class SES, a similar trend was observed. However, after performing additional adjustments for potential confounders, only associations comparing lower and upper middle class SES remained statistically significant (fully adjusted RRR of frailty 3.81, 95% CI 1.69, 8.58; p=0.001).

Table 15 *Relative risk ratios of frailty and pre-frailty according to childhood SES compared to the non-frail individuals of the cohort.*

	Model 1[a]		Model 2[b]		Model 3[c]	
	RRR (95% CI)	**p**	**RRR (95% CI)**	**p**	**RRR (95% CI)**	**p**
Childhood SES						
Upper middle class (Ref.)						
Lower middle class						
Non-frailty	Ref.		Ref.		Ref.	
Pre-frailty	1.14 (0.84, 1.55)	0.416	1.08 (0.79, 1.48)	0.618	1.12 (0.81, 1.55)	0.488
Frailty	1.57 (0.67, 3.70)	0.302	1.49 (0.62, 3.57)	0.368	1.36 (0.55, 3.36)	0.508
Manual workers						
Non-frailty	Ref.		Ref.		Ref.	
Pre-frailty	1.46 (1.05, 2.04)	0.025	1.30 (0.92, 1.84)	0.135	1.25 (0.88, 1.78)	0.223
Frailty	2.04 (0.77, 5.42)	0.153	1.57 (0.57, 4.35)	0.384	1.12 (0.39, 3.23)	0.837

Note. RRR=relative risk ratio, CI=confidence interval, SES=socioeconomic status. [a] Adjusted for sex and age. [b] Adjusted for Model 1 plus adult SES. [c] Adjusted for Model 2 plus adult BMI, smoking, hypertension and diabetes.

Table 16 *Relative risk ratios of frailty and pre-frailty according to adult SES compared to the non-frail individuals of the cohort.*

	Model 1[a]		Model 2[b]		Model 3[c]	
	RRR (95% CI)	**p**	**RRR (95% CI)**	**p**	**RRR (95% CI)**	**p**
Adulthood SES						
Upper middle class (Ref.)						
Lower middle class						
Non-frailty	Ref.		Ref.		Ref.	
Pre-frailty	1.50 (1.10, 2.05)	0.010	1.47 (1.08, 2.01)	0.016	1.35 (0.98, 1.87)	0.067
Frailty	4.26 (1.97, 9.24)	<0.001	4.11 (1.89, 8.97)	<0.001	3.81 (1.69, 8.58)	0.001
Self-employed						
Non-frailty	Ref.		Ref.		Ref.	
Pre-frailty	1.73 (1.06, 2.84)	0.030	1.63 (0.99, 2.69)	0.055	1.70 (1.01, 2.88)	0.047
Frailty	4.31 (0.97, 19.17)	0.055	3.85 (0.86, 17.35)	0.079	4.27 (0.92, 19.82)	0.064

Manual workers						
Non-frailty	Ref.		Ref.		Ref.	
Pre-frailty	1.82 (1.23, 2.68)	0.003	1.68 (1.12, 2.50)	0.012	1.46 (0.96, 2.22)	0.074
Frailty	3.18 (1.15, 8.80)	0.026	2.71 (0.94, 7.77)	0.064	2.41 (0.79, 7.32)	0.120

Note. RRR=relative risk ratio, CI=confidence interval, SES=socioeconomic status. [a] Adjusted for sex and age. [b] Adjusted for Model 1 plus childhood SES. [c] Adjusted for Model 2 plus adult BMI, smoking, hypertension and diabetes.

5.5 TELOMERE LENGTH, TELOMERE SHORTENING AND FRAILTY

The cohort members' telomere measurements are presented in Table 17. Women had longer relative LTL at both the mean age of 61 years (1.42 and 1.37 T/S units) and 71 years (0.90 and 0.81 T/S units) compared to the men (p-values<0.03). On average, relative LTL was 37.1% (SD 24.5) shorter compared to that measured 10 years earlier, with men losing on average a greater percentage of their relative LTL than women (p=0.006).

Table 17 *Measurements of telomere length and telomere shortening in the cohort.*

	Whole cohort		Men		Women		
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**p[a]**
Telomere length							
LTL at 61 years (T/S ratio)	1042	1.40 (0.29)	458	1.37 (0.29)	584	1.42 (0.29)	0.029
LTL at 71 years (T/S ratio)	1061	0.86 (0.30)	465	0.81 (0.27)	596	0.90 (0.32)	<0.001
Telomere shortening rate							
Between 61-71 years (change T/S ratio)	1037	-0.54 (0.36)	455	-0.57 (0.35)	582	-0.52 (0.37)	0.047
Between 61-71 years (change T/S ratio percent)	1037	-37.1 (24.5)	455	-39.5 (23.2)	582	-35.3 (25.3)	0.006

Note. SD=standard deviation, LTL=leukocyte telomere length. [a] Difference between men and women.

A graded decreasing trend in relative LTL was observed among non-frail, pre-frail and frail individuals with the mean age of 61 years (p^{trend}=0.016) and 71 years (p^{trend}=0.057) in the whole cohort (Figure 6). Cross-group comparisons between the non-frail and frail participants were borderline significant at both time points (both p-values=0.064). However, no trend in T/S shortening rate, expressed as either absolute or percentage change, was observed across frailty groups (p-values>0.500).

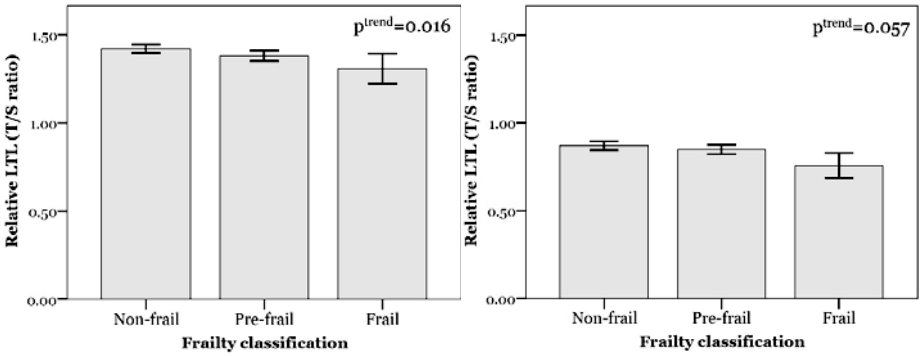

Figure 6 Relative T/S ratio measurements among non-frail, pre-frail and frail individuals at the mean ages of 61 and 71 years for the entire cohort. The error bars indicate confidence intervals set at 95%.

Relative LTL in people with the mean age of 61 years was associated with frailty in people with the mean age of 71 years, illustrated in Table 18. A one-unit increase in the T/S ratio corresponded with a decreased risk of frailty (RRR 0.24, 95% CI 0.07, 0.83; p=0.024) when non-frailty was selected as the reference category in age- and sex-adjusted analyses. The association was little changed after further adjustment for adult SES, body fat percentage, smoking habits, cardiovascular disease and diabetes, RRR being 0.28 (95% CI 0.08, 0.97; p=0.045).

An inverse association between relative LTL and frailty at the mean age of 71 years was observed, adjusting for age and sex. Per each unit increase in the T/S ratio the RRR of frailty was 0.16 (95% CI 0.04, 0.73; p=0.018) compared to the non-frail individuals. Further adjustments for confounders (RRR 0.25, 95% CI 0.06, 1.10; p=0.067) as well as relative LTL at the mean age of 61 years (RRR 0.27, 95% CI 0.06, 1.26; p=0.096) resulted in attenuation of the association between relative LTL and frailty at the average age of 71 years.

Table 18 *Relative risk ratios of frailty according to increasing telomere length and shortening.*

	Model 1[a]		**Model 2[b]**	
	RRR (95% CI)	**p**	**RRR (95% CI)**	**p**
LTL at the mean age of 61 years				
Non-frail	Ref.		Ref.	
Pre-frail	0.65 (0.42, 1.01)	0.057	0.69 (0.43, 1.10)	0.117
Frail	0.24 (0.07, 0.83)	0.024	0.28 (0.08, 0.97)	0.045
LTL at the mean age of 71 years				
Non-frail	Ref.		Ref.	
Pre-frail	0.82 (0.54, 1.26)	0.371	0.87 (0.56, 1.36)	0.549
Frail	0.16 (0.04, 0.73)	0.018	0.25 (0.06, 1.10)	0.067
LTL at the mean age of 71 years[c]				

Non-frail	Ref.		Ref.	
Pre-frail	0.92 (0.59, 1.43)	0.710	0.95 (0.60, 1.51)	0.824
Frail	0.27 (0.06, 1.26)	0.096	0.39 (0.09, 1.78)	0.138
T/S ratio percent shortening between 61 and 71 years[c]				
Non-frail	Ref.		Ref.	
Pre-frail	1.00 (0.99, 1.01)	0.963	1.00 (0.99, 1.01)	0.890
Frail	0.98 (0.96, 1.00)	0.075	0.99 (0.97, 1.01)	0.188

Note. RRR=relative risk ratio, LTL=leukocyte telomere length, SES=socioeconomic status. [a] Adjusted for sex and age. [b] Adjusted for Model 1 plus adult SES, adult body fat percentage, smoking, cardiovascular disease and diabetes. [c] Adjusted additionally for LTL at the mean age of 61 years.

The association between relative LTL and telomere shortening and frailty was further studied for the individual frailty criteria. While no associations between telomere measurements and *exhaustion, weight loss, low physical activity* and *weakness* were observed, the criterion of *slowness* seemed to be driving the association between telomere measurements and frailty (Table 19). This association was different for men and women, as indicated by the interactions between sex and telomere measurements on *slowness* (interaction p-values <0.05). In women, a one-unit increase in the relative LTL T/S ratios at 61 and 71 years were associated with *slowness* (age-adjusted OR's 0.30, 95% CI 0.14, 0.63; p=0.002 and 0.40, 95% CI 0.19, 0.87; p=0.020, respectively). The association between relative LTL at the mean age of 61 years and *slowness* changed only little after further adjustment for potential confounders, OR 0.33 (95% CI 0.15, 0.73; p=0.006), however, the association between LTL measured at the average of 71 years and *slowness* was attenuated after additional adjustment. This was not observed in men. No associations between telomere shortening and *slowness* were observed.

Table 19 *Odds ratios of fulfilling the frailty criterion of slowness according to increasing telomere length and shortening.*

	Model 1[a]		**Model 2[b]**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Frailty criterion of *slowness*				
LTL at the mean age of 61 years				
Whole cohort	0.39 (0.28, 0.69)	0.001	0.42 (0.23, 0.76)	0.004
Men	0.55 (0.24, 1.26)	0.157	0.52 (0.21, 1.29)	0.158
Women	0.30 (0.14, 0.63)	0.002	0.33 (0.15, 0.73)	0.006
LTL at the mean age of 71 years				
Whole cohort	0.64 (0.36, 1.12)	0.117	0.72 (0.40, 1.29)	0.271
Men	1.24 (0.54, 2.87)	0.610	1.10 (0.45, 2.69)	0.833
Women	0.40 (0.19, 0.87)	0.020	0.51 (0.23, 1.13)	0.096
LTL at the mean age of 71 years[c]				
Whole cohort	0.85 (0.48, 1.48)	0.560	0.93 (0.52, 1.66)	0.794

Men	1.40 (0.61, 3.22)	0.429	1.24 (0.51, 3.04)	0.637
Women	0.60 (0.28, 1.30)	0.195	0.74 (0.33, 1.63)	0.449
T/S ratio percent shortening between 61 and 71 years[c]				
Whole cohort	0.99 (0.99, 1.00)	0.496	0.99 (0.99, 1.01)	0.832
Men	1.01 (0.99, 1.02)	0.310	1.00 (0.99, 1.02)	0.417
Women	0.99 (0.98, 1.00)	0.097	0.99 (0.99, 1.01)	0.302

Note. OR=odds ratio, LTL=leukocyte telomere length, SES=socioeconomic status. [a] Adjusted for sex and age. [b] Adjusted for Model 1 plus adult SES, adult body fat percentage, smoking, cardiovascular disease and diabetes. [c] Adjusted additionally for LTL at the mean age of 61 years.

6 DISCUSSION

6.1 MAIN FINDINGS

The present study investigated frailty from a life-course perspective. Maternal characteristics and body size at birth represented prenatal influences. Serial measurements of weight and height from birth to childhood provided information on postnatal growth. Data on childhood SES was available and the social context of the study enabled us to study the effects of ELS on frailty in old age. The effects of adult SES were also studied. Ageing was studied at the cellular level by investigating the associations between LTL at the mean ages of 61 and 71 years and telomere shortening and frailty.

The results indicate that body size at birth was inversely associated with the incidence of frailty in that the higher the body size was at birth the lower the relative risk of frailty was compared to non-frailty. No associations between maternal BMI or birth order and frailty were observed. The boys who later became frail men experienced on average accelerated BMI growth in childhood (2-11 years) compared to the non-frail men. The girls who became frail women experienced growth that followed the cohort mean which was considered normal.

Wartime separation from both parents in childhood, a severe form of ELS, was associated with frailty in boys. These results suggest that among boys, younger age at and longer duration of the separation could amplify the harmful effects of ELS on frailty. Adult SES was associated with frailty showing an increased risk of frailty for individuals who as adults worked in manual labour occupations compared to those who had worked as officials. Childhood SES was not related to frailty in older age.

Finally, shorter LTL at 61 years was associated with an increased risk of frailty at the mean age of 71 years in prospective analyses. Similarly, a cross-sectional association between shorter LTL and frailty at 71 years was observed. Telomere shortening during the 10-year follow-up, however, was not associated with frailty at the mean age of 71 years.

6.2 INTERPRETATION OF THE RESULTS

6.2.1 EARLY LIFE DETERMINANTS OF FRAILTY IN OLD AGE

Based on the DOHaD hypothesis we hypothesized that maternal obesity, small body size at birth and being first born would result in increased risk of frailty in old age. We observed that the findings regarding body size at birth were in accordance with the hypothesis.

Small body size at birth i.e. low weight, height and BMI at birth, may affect later health through the phenomenon known as programming (21). When nutrition is inadequate the foetus acts to prioritize growth of vital organs at the expense of others. For example, vital tissues in the central nervous system such as the brain can be prioritized over tissues in the musculoskeletal system. Babies who are born small have less fat-free mass (88), a higher prevalence of sarcopenia (108) and are less physically active as adults (110). Furthermore, small babies are at an increased risk of several chronic diseases (Table 1). The overlap between frailty, a geriatric syndrome, and comorbidity, which indicates the simultaneous prevalence of any two or more chronic disease, has been illustrated in the definition of frailty by Fried and colleagues (2). On the one hand, a higher chronic disease burden is likely to result in poorer functioning in part through prolonged activity of mechanisms involving e.g. chronic inflammation. On the other, when these diseases manifest acutely, a more rapid progression of frailty could be expected due to inability to respond to a stressor.

The birth weight of the newly born is generally considered to increase with increasing birth order (274,275). In the present study, first born children did not differ from second or later born children in terms of frailty in old age. This could indicate that changes in birth weight, assuming that the siblings share the same living environment, would not result in detectable changes in frailty in first versus later born children, given that also several other factors contribute to birth weight (Figure 2).

Maternal obesity, defined as a high BMI (BMI>30kg/m^2) recorded during pregnancy, has been linked with a higher prevalence of chronic diseases in the offspring (276,277). However, no association between maternal BMI and frailty was observed in the present study. It is of note that maternal obesity was relatively uncommon at the time the mothers of the study cohort members were pregnant in the 1930s and 1940s.

6.2.2 GROWTH AND FRAILTY IN OLD AGE

According to the DOHaD hypothesis, key aspects of growth that predispose an individual to chronic disease include the concept of mismatch. Essentially, growth is mismatched when postnatal circumstances are not aligned with what was programmed *in utero*. An example of mismatched growth would be prenatal undernutrition followed by excess of nutrition after birth.

In the present study, the association between postnatal growth and frailty in old age was relatively weak. No associations between size at 1, 2, 7 and 11 years and frailty were observed. Furthermore, growth from birth to the age of 2 years was not associated with frailty in old age. However, growth in childhood, i.e. from age 2 to 11 years, was associated with frailty showing distinct patterns of growth among boys and girls who later became frail men and women.

The growth of boys who later became frail men was mismatched. They were small at birth after which they caught up reaching beyond the cohort average in childhood. In late childhood, their mean Z-scores of BMI and weight were more than 0.3 SD above the cohort average, whereas their mean Z-scores of height were below the cohort average. The concept of mismatch is further illustrated in the prevalence of frailty according to categories of birth weight and BMI at age 11. The prevalence of frailty was observed to be highest among those who as newborns belonged to the group with the lowest birth weight, and at the age of 11 years, to the group with the highest BMI.

The increase in BMI without marked increases in mean height suggest that the increase in BMI would primarily be attributed to increases in adiposity. There is evidence of a strong association between childhood obesity and obesity in adult life (278–280). Childhood obesity may have harmful and long-lasting effects on adult morbidity (281,282). Conversely, the boys who later became frail men had often been small at birth. In late adulthood, obesity together with loss of lean mass may result in a form of obesity that is characterized with sarcopenia, 'sarcopenic obesity', which is associated with frailty (283).

An interesting observation from the present study is that besides adiposity, postnatal growth could also be associated with frailty. While the association between BMI gain and frailty was attenuated in boys in the final model, further adjustment for adult BMI resulted in little further attenuation in the association. This could mean that postnatal BMI gain could have modest independent effects on frailty in old age, i.e. effects that would not be mediated through BMI in adulthood. While frailty is more common among individuals with extremely low or high adult BMI, waist circumference has been observed to be associated with frailty even in ranges of normal BMI in that individuals with higher waist circumferences would be at increased risk of frailty (284). In the present study, a trend of increasing BMI with increasing grade of frailty was observed. Among frail individuals, BMI has been observed to mediate levels of inflammatory markers that lie on the pathway to ageing-related chronic disease (285,286).

The pattern of growth in the frail men in the present study resembles that observed for other chronic diseases. Therefore, it is possible that the pattern of growth to frailty would be linked with chronic diseases, especially because of attenuation of the association after controlling for key chronic diseases.

Another important point to address is the observed sex difference. Accelerated BMI growth in childhood was associated with frailty in boys only; the girls who later became frail women experienced growth within the normal range. Possible candidates for this difference include variation in sex hormones that would result in distinct body compositions with individuals in similar ranges of childhood BMI. Besides sex hormones, various environmental and epigenetic mechanisms are likely to contribute to the observed associations. However, due to the small numbers of frail men (n=13)

and women (n=26) the possibility of a chance finding cannot be excluded. Thus, the findings from the present study should be interpreted with caution.

6.2.3 EARLY LIFE STRESS AND FRAILTY IN OLD AGE

There is evidence linking stressful early life events with later health outcomes. The contribution of ELS has been most studied regarding psychiatric outcomes. Less is known whether ELS is associated with frailty. Based on the long-term associations between ELS and cortisol metabolism (287), inflammation (288) and telomere length (289), we hypothesized that ELS would predispose an individual to ageing-related disease and frailty. Furthermore, based on previous evidence on the association between age at and duration of ELS and later health outcomes (266), we hypothesized that younger age at and longer duration of wartime separation would further accentuate the harmful contribution of ELS.

An association between ELS and frailty was observed in men only. No associations were observed in women. Among men, earlier age at and longer duration of the separation were associated with increased risk of frailty. The frailty criterion of *weakness* seemed to be driving the association between ELS and frailty. The findings showed an increased risk of fulfilling the criterion of *weakness* for the separated men but a decreased risk of fulfilling the criterion for the separated women.

Evidence on the multiple effects that stress has on biological systems come from experiments done in animals (290). In ELS, stressful life experiences occur within a period in development that can be considered critical for later development. Systems that are characterized with high plasticity can be affected when facing these stressful events and programmed for later life. The effects of stress are best known for hormonal pathways e.g. the HPA-axis (121). On the other hand, ELS has also been associated with higher levels of inflammatory markers among adults (288). Lower levels of inflammatory markers are in fact measured among those who experience close relationships in their lives (291). Among war evacuees in the present study, close relationships and parental relations could have been disrupted. The new foster environment is likely to have had gene-environment interactions with the evacuees' genetic factors and affected some more than others based on their genetic susceptibility. There is evidence to support susceptibility based on genetics on stress-related outcomes including depression (292). It is also possible that the experience of ELS could on its own result in changes in gene expression (293).

We did not hypothesize that the effects of ELS would depend on sex. However, there is mounting evidence of a sex difference in stress responsiveness where men would be more prone to the harmful effects of ELS than women (294,295). Previous evidence from the HBCS suggests that cortisol metabolism is altered in a sex-depended manner among separated individuals with men reacting more powerfully to a stress test (287). When the

association between ELS and physical and psychosocial functioning was studied in the HBCS, lower functioning scores were observed among separated men than non-separated men but this was not observed among the women in the cohort (266). Another thing to support the existence of a sex difference are the different 95% CI's of risks of frailty for the men and women in the cohort.

6.2.4 TELOMERE LENGTH AND FRAILTY IN OLD AGE

Short LTL plays a role in chronic disease pathology. Research on telomere biology supports the use of LTL as an ageing biomarker i.e. that it could give insight to the organism's biological age (296). Frailty, a multi-dimensional geriatric syndrome, has been suggested to be a clinical presentation of advanced biological age (297). We hypothesized that phenomena describing both cellular and clinically detectable ageing would be associated with each other and that those with short LTL would be at risk of frailty. Furthermore, it was hypothesized that greater telomere shortening during a given period would result in accelerated cellular and even clinically detectable ageing and frailty.

In the present study, short LTL was associated with frailty in prospective and cross-sectional analyses. This contradicts evidence from previous cross-sectional studies where no associations were observed. However, during and after the publication of results from the present study, evidence of an association between LTL and frailty is also increasing. The absence of previously observed associations could result from the use of only one LTL measurement in large populations where great variability in biological ageing and LTL is expected.

Results from the present study support the role of LTL as a frailty biomarker in its ability to detect frailty-related processes. Associations between frailty criteria and LTL suggest that short LTL could be associated with aspects of physical performance including walking speed and grip strength. Moreover, short LTL may increase risk of chronic disease and multimorbidity, a state in which an individual is at increased risk of depletion of homeostatic reserves, potentially giving rise to frailty. At the cellular level, individuals with critically short telomeres are at an increased risk of senescence, which is a state characterized by cellular dysfunction, secretion of inflammatory markers and increased oxidative stress (298–300). These factors, namely markers of inflammation and oxidative stress, have been observed to be higher among frail older individuals (285,301).

We hypothesized that telomere shortening would be observed more clearly among frail than non-frail individuals at the end of the follow-up. However, no such association was observed in the present study. This could be the result of the dependence of telomere shortening on initial telomere length i.e. that individuals experiencing more telomere shortening would also have had long telomeres at baseline (152). Essentially, individuals undergoing accelerated

telomere shortening would not necessarily have short LTL which would put their cells at risk of senescence.

Evidence from one of the largest studies assessing age-associated telomere shortening suggests that most of telomere shortening would occur during the first decades of life after which the rate of telomere shortening would be relatively fixed (151). In the present study, the strength of prospective associations was not attenuated in the final model in contrast to cross-sectional findings which were attenuated. LTL has not been found to be associated with frailty in the oldest old, which may indicate a more purposeful use of LTL measured at younger ages in detecting individuals that are at-risk of frailty.

6.3 STRENGTHS AND LIMITATIONS OF THE STUDY

Epidemiological cohort studies can demonstrate associations between multiple exposures and outcomes as well as provide estimates of prevalence and incidence. Birth cohorts are longitudinal studies that follow participants born during a certain time throughout their lives. Essentially, during this time a proportion of individuals are exposed to certain factors while others are not, and these groups are then followed up to determine the associations between exposures and the outcome. Although the analyses were controlled for potential confounders, some unmeasured confounding might still be present.

A major strength of the present study is the rich and diverse information available for the cohort. Several variables across the life-course could be extracted for more than 1,000 individuals. Hospital birth records provided information with minimal bias on the circumstances that took place at birth. Records held at child welfare clinics and schools had information on serial measurements of anthropometry. On average, 17 measurements of body size were available for each individual from birth to the age of 12 years. Information on the participants' socioeconomic circumstances and adult working history were obtained from Statistics Finland.

The Finnish Government has registers containing information on wartime evacuations conducted during WWII, and through these registers, reliable information on both the age at and duration of the separation was available. However, no information on the quality of foster care was available from these registers. Not all evacuations were performed through the Government, and to find these individuals of whom no register information was available, questionnaires on wartime separation were administered at the clinical study visits. Of note is also the fact that not all evacuees returned to Finland from their foster families. Moreover, given this few observations of frail separated men (n=4) and women (n=2), the possibility of a chance finding cannot be excluded and thus the findings should be considered as preliminary.

A key strength of the study is the use of 2 LTL measurements. The observed interassay variability was particularly high (CV 21 %) at the baseline LTL

measurement. Some previous studies adjusted the analyses further with levels of inflammatory markers, which was not done in the present study due to the low sample size of frail individuals with information on inflammation.

The main outcome variable of frailty was defined according to the criteria put forward by Fried and colleagues (2) using minor modifications. The use of an established frailty definition enables comparison with studies utilizing the same definition. Given the strict cut-offs used in the definition of frailty in the present study, the subsequent prevalence of frailty was lower than in other studies with participants of similar age (302,303). The low number of frail individuals was particularly challenging for the interpretation of results regarding early growth and ELS. We expect the number of frail individuals to increase as the cohort ages. Frailty was first measured at the follow-up clinical examination, and while it is uncertain that measuring frailty at baseline would have captured any frail individuals, it would be insightful in studying transitions between frailty classes. The used frailty definition has also received criticism for not including information on cognitive status, which has been considered in more recent definitions (304).

The cohort members were followed up to the mean age of 71 years in the present study. This extensively long follow-up together with clinical data enabled us to study associations between various factors during the life-course and frailty in old age. The long follow-up, however, gives rise to a host of confounding factors. Thus, the possibility of remaining uncontrolled confounding cannot be excluded. The analyses were adjusted for key lifestyle factors and chronic diseases.

While all participants had been born in Helsinki between the years 1934 and 1944, only those who visited child welfare clinics during those times were included. Similarly, participation in the baseline and follow-up clinical examinations was voluntary. At every step, those in poor health may have been less keen on participating, resulting in loss to follow-up, selective survival and an underrepresentation of frail individuals. Therefore, associations found in the study could be underestimations.

The world is quite different now in comparison with what it was in the 1930's and 1940's. Finland, having gone through rapid industrialization, has transitioned from a developing to a highly developed country. Similarly, the availability of food and eating culture as a whole have undergone considerable changes. For example, for the present cohort, undernutrition may have been a bigger problem than for more contemporary cohorts battling with childhood obesity. Cohort effects may limit generalizability of the results to other more contemporary populations.

6.4 IMPLICATIONS OF THE FINDINGS

Results from the present study add to the understanding of frailty and of the contribution that early life risk factors have on the syndrome. The associations

between body size at birth and frailty suggest that susceptibility to frailty may be programmed as early on as *in utero*. The influence of the prenatal environment on frailty was modified by postnatal growth, however to a minor extent. Early life stress was associated with frailty in men only. This vulnerability found particularly in men could be the result of reprogramming of the HPA-axis and consequent changes to cortisol metabolism. The association between LTL and frailty implies that cellular senescence and lifespan may be involved in the cellular mechanisms that eventually may give rise to clinical frailty. LTL could be a meaningful frailty biomarker.

Chronic disease prevention should start at a younger age. Studying chronic diseases from a life-course perspective gives insight into the importance of different risk factors during different sensitive periods in the life-course. Through promotion of health of the mother, her baby, and consequent growth of the infant and child, the risk of later chronic disease and frailty may be reduced. The information provided in this thesis can be used to identify at-risk groups of individuals who may have an increased risk of chronic illnesses and who may benefit from disease prevention.

6.5 IMPLICATIONS FOR FUTURE STUDIES

Cohort effects and the historical context of the present study may limit the generalizability of the results. However, in birth cohorts worldwide, the incidence of frailty is very low given the fact that frailty starts to become increasingly prevalent after the 7th decade. The findings should be confirmed in more contemporary cohorts.

The proportion of frail individuals is expected to increase as the mean age of HBCS participants increases. Follow-up studies may have enough power to clarify the sex differences found regarding early growth and early life stress. The low proportion of frail individuals in the cohort may have limited the interpretation of the results. The third clinical examination of the cohort members, which is ready by the end of year 2018, will enable analyses that explore change in frailty longitudinally within the same individuals and the contribution of life course risk factors on transitions between frailty categories. This would be particularly interesting regarding study IV where more high-quality studies are needed to determine whether short LTL precedes frailty.

Besides studying associations between early predictors and frailty in old age it would be of interest to investigate the future health of frail participants of the cohort. Longitudinal studies between frailty and clinical measurements including blood pressure, glucose tolerance and cholesterol levels could give insight into the effects of frailty on commonly used health indicators.

7 CONCLUSIONS

The present study investigated frailty determinants from a life-course perspective. Following conclusions could be drawn from the studies:

1. Susceptibility to frailty may in part be programmed early in life, illustrated in the inverse association between body size at birth and frailty in old age.

2. Childhood SES was not associated with frailty but adult SES was, suggesting that those with poor socioeconomic status in adult life could be at an increased risk of frailty.

3. The growth of boys who became frail men was mismatched showing increased BMI gain in childhood. The association was independent of adulthood BMI.

4. Boys experiencing ELS were more often frail men in old age. No associations were observed among women, suggesting that the association between ELS and frailty could vary by sex.

5. LTL was associated with frailty in prospective and cross-sectional analyses, suggesting that cellular lifespan and senescence could be involved in frailty pathophysiology. Furthermore, the results suggest that LTL could be a useful frailty biomarker in that it could detect frailty-related processes.

8 ACKNOWLEDGEMENTS

This work was carried out within the Public Health Programme of Folkhälsan Research Center at the Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, between the years 2017 and 2019. I wish to acknowledge Head of Department Kaisu Pitkälä and Program Director Johan Eriksson for providing excellent research facilities.

This study was financially supported by grants from Samfundet Folksälsan i svenska Finland Foundation, the Finnish Medical Society Finska Läkaresällskapet, the Finnish Medical Society Duodecim and Liv och Hälsa Foundation. The University of Helsinki Chancellor's travel grant and the 14th EuGMS Young Researcher travel grant enabled the presentation of the results in international congresses.

It has been a privilege to work with two inspiring and supportive thesis supervisors. Professor Johan Eriksson, who first introduced me to this interesting thesis project, has provided me with continuous support and advice throughout the time we have worked together. Your encouragement and cheering during my first presentation have given me confidence to go on to enjoy giving out presentations. Johan, thanks to you my ability of writing and speaking Swedish has rapidly caught up that of my mother tongue. Finally, I am truly grateful for your flexibility which gave me freedom to develop as a researcher.

Docent Mikaela von Bonsdorff, I acknowledge with immense gratitude all the time and hard effort you have put into giving me feedback during this project. Your scrutiny over my work has taught me a lot about scientific writing. Over the course of this project I have come to know you not only professionally as an incredibly capable person but also as a friend through shared moments. I sincerely thank you for believing in me and inviting me to participate in the preparation of manuscripts also outside of this thesis.

My sincere thanks go to the official reviewers of this thesis. Professor Riitta Antikainen and Associate Professor Anna-Maija Tolppanen, thank you for your time and effort in enabling improvement of my thesis.

I extend my warmest gratitude to all my co-authors. Mia-Maria Perälä, PhD, Minna Salonen, PhD, Docent Eero Kajantie, Academy Professor Katri Räikkönen, Docent Anu-Katriina Pesonen, Professor Taina Rantanen, Pertti Pohjolainen, PhD, Docent Patricia Iozzo, Maria Angela Guzzardi, PhD, and Professor Clive Osmond, thank you for the helpful comments and suggestions that enabled improvement of the study.

I am glad to have had the chance to develop my clinical skills during my time off the project. The ward at Loviisa health care center has proved me with valuable experience that has helped me grow as a physician. My special thanks go to all the nurses, and to my consultants Juuso Ylärakkola, MD, and

Katariina Borup, MD, for helping me through my first summer working as a physician.

The friendly atmosphere among co-workers at the Department of General Practice and Primary Health Care has made it easy to have both nice conversations and seek help regarding the project. Lena Sjöberg, thank you for the discussions on literature and chocolate as well as the language revision of the Swedish abstract. Anita Valkama, Jelena Meinilä and Jemina Kivelä, thank you for the support. A special thanks to Niko Perttilä, with whom I have not only had the pleasure of working with but also attending congresses across Europe.

The support and company of close friends has been of immense personal importance and value to me. Jenni Ikonen, what would have our lives been had we not bumped to one another that cold afternoon in February. The countless conversations with Jan Frilander about everything conceivable have resulted in tremendous personal growth. Kjel Klaver, thank you for the many walks and dinners throughout the making of this thesis.

Had it not been for that silly Vietnamese card game I would never have been a part of a group of friends that go by the name of The Society of Albino Asians. Vinh Chau, Ali Lashdaf, Leevi Valkeavirta, Toivo Korhonen, Jere Hupanen and Joonas Törmänen, our friendship has endured while seemingly almost everything else has changed with passing years. I am looking forward to our next adventures. Helsingin Ruokainsinöörit, thank you for the many evenings of ethnic cooking, photography and music.

The design and layout of the thesis cover is the work of Saana Pitkänen. I feel privileged to have had the possibility of providing a platform for her artistic talent. Having known Saana and her sister Peppiina for a decade now I am also grateful to consider them as dear friends with whom there never is a dull moment.

A warm thanks to all my classmates at the Faculty of Medicine and Cursus Medicorum Aeternalium for sharing experiences and struggles related to both medicine and life in general. Lotta Mäkinen, Johan Roos, Katariina Lahtinen, Atte Lahtinen, Eero Ala-Mutka, Veli-Matti Uhre, Heikki Annala, Abdessalam Tadji, Anni Parviainen and Lauri Saksa, thank you for the many shared laughs during medical school. A special and sincere thanks to Jenna Kauhanen and Petro Kyrylenko for their friendship and support.

Finally, I want to thank my parents and little brother Henri for their unconditional love and support. While you most probably had little understanding of what I was doing, you always listened with patience to what news I had regarding the project. You have been and always will be of key importance to me.

9 REFERENCES

1. United Nations, Department of Economic and Social Affairs PD. *World Population Prospects: The 2015 Revision, Key Findings and Advance Tables. Working Paper No. ESA/P/WP.241*. New York; 2015.
2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56. http://www.ncbi.nlm.nih.gov/pubmed/11253156. Accessed March 11, 2017.
3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet (London, England)*. 2013;381(9868):752-762. doi:10.1016/S0140-6736(12)62167-9.
4. Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunananthan S, Wolfson C. Frailty: an emerging research and clinical paradigm--issues and controversies. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):731-737. http://www.ncbi.nlm.nih.gov/pubmed/17634320. Accessed March 24, 2017.
5. Chang S-F, Lin P-L. Frail phenotype and mortality prediction: A systematic review and meta-analysis of prospective cohort studies. *Int J Nurs Stud*. 2015;52(8):1362-1374. doi:10.1016/j.ijnurstu.2015.04.005.
6. Kojima G. Frailty as a Predictor of Nursing Home Placement Among Community-Dwelling Older Adults. *J Geriatr Phys Ther*. 2018;41(1):42-48. doi:10.1519/JPT.0000000000000097.
7. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. *Disabil Rehabil*. 2017;39(19):1897-1908. doi:10.1080/09638288.2016.1212282.
8. Kojima G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. *J Epidemiol Community Health*. 2016;70(7):722-729. doi:10.1136/jech-2015-206978.
9. Kojima G. Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis. *Bone*. 2016;90:116-122. doi:10.1016/j.bone.2016.06.009.
10. Kojima G. Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc*. 2015;16(12):1027-1033. doi:10.1016/j.jamda.2015.06.018.
11. Cesari M, Prince M, Thiyagarajan JA, De Carvalho IA, Bernabei R, Chan P, Gutierrez-Robledo LM, Michel J-P, Morley JE, Ong P, Rodriguez Manas L, Sinclair A, Won CW, Beard J, Vellas B. Frailty: An Emerging Public Health Priority. *J Am Med Dir Assoc*. 2016;17(3):188-192. doi:10.1016/j.jamda.2015.12.016.
12. Fugate Woods N, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, Masaki K, Murray A, Newman AB. Frailty: Emergence and Consequences in Women Aged 65 and Older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2005;53(8):1321-1330. doi:10.1111/j.1532-5415.2005.53405.x.

13. Ottenbacher KJ, Graham JE, Al Snih S, Raji M, Samper-Ternent R, Ostir G V., Markides KS. Mexican Americans and Frailty: Findings From the Hispanic Established Populations Epidemiologic Studies of the Elderly. *Am J Public Health*. 2009;99(4):673-679. doi:10.2105/AJPH.2008.143958.
14. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review. *Br J Clin Pharmacol*. 2018;84(7):1432-1444. doi:10.1111/bcp.13590.
15. Kuh D. A Life Course Approach to Healthy Aging, Frailty, and Capability. *Journals Gerontol Ser A Biol Sci Med Sci*. 2007;62(7):717-721. doi:10.1093/gerona/62.7.717.
16. Kuh D, Karunananthan S, Bergman H, Cooper R. A life-course approach to healthy ageing: maintaining physical capability. *Proc Nutr Soc*. 2014;73(2):237-248. doi:10.1017/S0029665113003923.
17. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health*. 2003;57(10):778-783. http://www.ncbi.nlm.nih.gov/pubmed/14573579. Accessed March 11, 2017.
18. Barker DJP, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med*. 2005;353(17):1802-1809. doi:10.1056/NEJMoa044160.
19. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of In Utero and Early-Life Conditions on Adult Health and Disease. *N Engl J Med*. 2008;359(1):61-73. doi:10.1056/NEJMra0708473.
20. Forsén T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D. The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Intern Med*. 2000;133(3):176-182. http://www.ncbi.nlm.nih.gov/pubmed/10906831. Accessed April 20, 2018.
21. Lucas A. Programming by early nutrition in man. *Ciba Found Symp*. 1991;156:38-50; discussion 50-5. http://www.ncbi.nlm.nih.gov/pubmed/1855415. Accessed April 25, 2017.
22. Barker DJP. *Mothers, Babies and Health in Later Life*. 2nd ed. Edinburgh: Churchill Livingstone; 1998. ISBN:0443061653 (pbk.).
23. Barraclough CA. Production of anovulatory, sterile rats by single injections of testosterone propionate. *Endocrinology*. 1961;68(1):62-67. doi:10.1210/endo-68-1-62.
24. Roeder LM. Effect of the level of nutrition on rates of cell proliferation and of RNA and protein synthesis in the rat. *Nutr Rep Int*. 1973;7:271-287.
25. Hales CN, Desai M, Ozanne SE, Crowther NJ. Fishing in the stream of diabetes: from measuring insulin to the control of fetal organogenesis. *Biochem Soc Trans*. 1996;24(2):341-350. http://www.ncbi.nlm.nih.gov/pubmed/8736760. Accessed November 16, 2018.
26. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet (London, England)*. 1986;1(8489):1077-1081. http://www.ncbi.nlm.nih.gov/pubmed/2871345. Accessed January 30, 2018.
27. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in

infancy and death from ischaemic heart disease. *Lancet (London, England)*. 1989;2(8663):577-580. http://www.ncbi.nlm.nih.gov/pubmed/2570282. Accessed January 30, 2018.

28. Barker DJP. Fetal origins of coronary heart disease. *BMJ*. 1995;311(6998):171-174. doi:10.1136/bmj.311.6998.171.
29. Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley RA, Gluckman P, Godfrey K, Kirkwood T, Lahr MM, McNamara J, Metcalfe NB, Monaghan P, Spencer HG, Sultan SE. Developmental plasticity and human health. *Nature*. 2004;430(6998):419-421. doi:10.1038/nature02725.
30. Gluckman PD, Hanson MA. Living with the Past: Evolution, Development, and Patterns of Disease. *Science (80-)*. 2004;305(5691):1733-1736. doi:10.1126/science.1095292.
31. Bertram CE, Hanson MA. Animal models and programming of the metabolic syndrome. *Br Med Bull*. 2001;60:103-121. http://www.ncbi.nlm.nih.gov/pubmed/11809621. Accessed April 18, 2018.
32. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev*. 2005;85(2):571-633. doi:10.1152/physrev.00053.2003.
33. Fowden AL, Giussani DA, Forhead AJ. Intrauterine Programming of Physiological Systems: Causes and Consequences. *Physiology*. 2006;21(1):29-37. doi:10.1152/physiol.00050.2005.
34. Suter M, Abramovici A, Aagaard-Tillery K. Genetic and epigenetic influences associated with intrauterine growth restriction due to in utero tobacco exposure. *Pediatr Endocrinol Rev*. 2010;8(2):94-102. http://www.ncbi.nlm.nih.gov/pubmed/21150839. Accessed April 18, 2018.
35. Moisiadis VG, Matthews SG. Glucocorticoids and fetal programming part 2: mechanisms. *Nat Rev Endocrinol*. 2014;10(7):403-411. doi:10.1038/nrendo.2014.74.
36. Fowden AL. Endocrine regulation of fetal growth. *Reprod Fertil Dev*. 1995;7(3):351-363. http://www.ncbi.nlm.nih.gov/pubmed/8606944. Accessed April 18, 2018.
37. Perälä M-M, Eriksson JG. Early growth and postprandial glucose, insulin, lipid and inflammatory responses in adulthood. *Curr Opin Lipidol*. 2012;23(4):327-333. doi:10.1097/MOL.0b013e3283541da6.
38. Delgado-Rodríguez M, Gómez-Olmedo M, Bueno-Cavanillas A, García-Martín M, Gálvez-Vargas R. Recall bias in a case-control study of low birth weight. *J Clin Epidemiol*. 1995;48(9):1133-1140. http://www.ncbi.nlm.nih.gov/pubmed/7636515. Accessed September 20, 2018.
39. Lumey LH, Stein AD, Ravelli AC. Maternal recall of birthweights of adult children: validation by hospital and well baby clinic records. *Int J Epidemiol*. 1994;23(5):1006-1012. http://www.ncbi.nlm.nih.gov/pubmed/7860151. Accessed September 20, 2018.
40. WHO. *Country, Regional and Global Estimates Low Birthweight*.; 2004. http://apps.who.int/iris/bitstream/handle/10665/43184/9280638327.pdf;jsessionid=9FB81238B48458CBF8EBE1B9167A05DA?sequence=1. Accessed September 20, 2018.

41. Kramer MS. *Determinants of Low Birth Weight: Methodological Assessment and Meta-Analysis 4828 663*. Vol 65.; 1987. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2491072/pdf/bullwh000076-0086.pdf. Accessed October 22, 2018.

42. Stein CE, Fall CH, Kumaran K, Osmond C, Cox V, Barker DJ. Fetal growth and coronary heart disease in south India. *Lancet (London, England)*. 1996;348(9037):1269-1273. http://www.ncbi.nlm.nih.gov/pubmed/8909379. Accessed April 22, 2018.

43. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, adult risk factors and incident coronary heart disease: the Caerphilly Study. *Public Health*. 1996;110(3):139-143. http://www.ncbi.nlm.nih.gov/pubmed/8668758. Accessed April 20, 2018.

44. Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, Willett WC, Hennekens CH. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ*. 1997;315(7105):396-400. http://www.ncbi.nlm.nih.gov/pubmed/9277603. Accessed April 20, 2018.

45. Leon DA, Lithell HO, Vâgerö D, Koupilová I, Mohsen R, Berglund L, Lithell UB, McKeigue PM. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. *BMJ*. 1998;317(7153):241-245. http://www.ncbi.nlm.nih.gov/pubmed/9677213. Accessed April 20, 2018.

46. Eriksson JG, Forsén T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ*. 1999;318(7181):427-431. http://www.ncbi.nlm.nih.gov/pubmed/9974455. Accessed April 20, 2018.

47. Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth Weight Is Inversely Associated With Incident Coronary Heart Disease and Stroke Among Individuals Born in the 1950s: Findings From the Aberdeen Children of the 1950s Prospective Cohort Study. *Circulation*. 2005;112(10):1414-1418. doi:10.1161/CIRCULATIONAHA.104.528356.

48. Huxley R, Owen CG, Whincup PH, Cook DG, Rich-Edwards J, Smith GD, Collins R. Is birth weight a risk factor for ischemic heart disease in later life? *Am J Clin Nutr*. 2007;85(5):1244-1250. doi:10.1093/ajcn/85.5.1244.

49. Wang S-F, Shu L, Sheng J, Mu M, Wang S, Tao X-Y, Xu S-J, Tao F-B. Birth weight and risk of coronary heart disease in adults: a meta-analysis of prospective cohort studies. *J Dev Orig Health Dis*. 2014;5(06):408-419. doi:10.1017/S2040174414000440.

50. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ*. 1989;298(6673):564-567. http://www.ncbi.nlm.nih.gov/pubmed/2495113. Accessed April 20, 2018.

51. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation*. 1996;94(12):3246-3250. http://www.ncbi.nlm.nih.gov/pubmed/8989136. Accessed April 22, 2018.

52. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ. Birth weight and adult hypertension and obesity in women. *Circulation*. 1996;94(6):1310-1315. doi:10.1161/01.CIR.94.6.1310.

53. Zhang Y, Li H, Liu S, Fu G, Zhao Y, Xie Y-J, Zhang Y, Wang Y. The associations of high birth weight with blood pressure and hypertension in later life: a systematic review and meta-analysis. *Hypertens Res*. 2013;36(8):725-735. doi:10.1038/hr.2013.33.

54. Martyn CN, Barker DJ, Osmond C. Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. *Lancet (London, England)*. 1996;348(9037):1264-1268. http://www.ncbi.nlm.nih.gov/pubmed/8909378. Accessed April 22, 2018.

55. Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJ. Early growth, adult income, and risk of stroke. *Stroke*. 2000;31(4):869-874. http://www.ncbi.nlm.nih.gov/pubmed/10753990. Accessed April 22, 2018.

56. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. *BMJ*. 1996;312(7028):406-410. http://www.ncbi.nlm.nih.gov/pubmed/8601111. Accessed April 20, 2018.

57. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsén T, Grill V, Gudnason V, Hulman S, et al. Birth Weight and Risk of Type 2 Diabetes. *JAMA*. 2008;300(24):2886. doi:10.1001/jama.2008.886.

58. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth Weight and Subsequent Risk of Type 2 Diabetes: A Meta-Analysis. *Am J Epidemiol*. 2007;165(8):849-857. doi:10.1093/aje/kwk071.

59. Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, Plagemann A. Birth Weight, Early Weight Gain, and Subsequent Risk of Type 1 Diabetes: Systematic Review and Meta-Analysis. *Am J Epidemiol*. 2009;169(12):1428-1436. doi:10.1093/aje/kwp065.

60. Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, Guo XR. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes Rev*. 2011;12(7):525-542. doi:10.1111/j.1467-789X.2011.00867.x.

61. Jacobsson LTH, Jacobsson ME, Askling J, Knowler WC. Perinatal characteristics and risk of rheumatoid arthritis. *BMJ*. 2003;326(7398):1068-1069. doi:10.1136/bmj.326.7398.1068.

62. Mandl LA, Costenbader KH, Simard JF, Karlson EW. Is birthweight associated with risk of rheumatoid arthritis? Data from a large cohort study. *Ann Rheum Dis*. 2009;68(4):514-518. doi:10.1136/ard.2007.080937.

63. Mostafavi B, Akyuz S, Jacobsson ME, Nilsen L V, Theander E, Jacobsson LH. Perinatal characteristics and risk of developing primary Sjögren's syndrome: a case-control study. *J Rheumatol*. 2005;32(4):665-668. http://www.ncbi.nlm.nih.gov/pubmed/15801022. Accessed April 22, 2018.

64. Gale CR, Martyn CN. Birth weight and later risk of depression in a national birth cohort. *Br J Psychiatry*. 2004;184:28-33. http://www.ncbi.nlm.nih.gov/pubmed/14702224. Accessed April 20, 2018.

65. De Mola CL, De França GVA, de Avila Quevedo L, Horta BL. Low birth weight, preterm birth and small for gestational age association with adult depression: systematic review and meta-analysis. *Br J Psychiatry*. 2014;205(05):340-347. doi:10.1192/bjp.bp.113.139014.

66. Wojcik W, Lee W, Colman I, Hardy R, Hotopf M. Foetal origins of depression? A systematic review and meta-analysis of low birth weight and later depression. *Psychol Med*. 2013;43(01):1-12. doi:10.1017/S0033291712000682.

67. Saad NJ, Patel J, Burney P, Minelli C. Birth Weight and Lung Function in Adulthood: A Systematic Review and Meta-analysis. *Ann Am Thorac Soc*. 2017;14(6):994-1004. doi:10.1513/AnnalsATS.201609-746SR.

68. Baird J, Kurshid MA, Kim M, Harvey N, Dennison E, Cooper C. Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. *Osteoporos Int*. 2011;22(5):1323-1334. doi:10.1007/s00198-010-1344-9.

69. Martínez-Mesa J, Restrepo-Méndez MC, González DA, Wehrmeister FC, Horta BL, Domingues MR, Menezes AMB. Life-course evidence of birth weight effects on bone mass: systematic review and meta-analysis. *Osteoporos Int*. 2013;24(1):7-18. doi:10.1007/s00198-012-2114-7.

70. White SL, Perkovic V, Cass A, Chang CL, Poulter NR, Spector T, Haysom L, Craig JC, Salmi I Al, Chadban SJ, Huxley RR. Is Low Birth Weight an Antecedent of CKD in Later Life? A Systematic Review of Observational Studies. *Am J Kidney Dis*. 2009;54(2):248-261. doi:10.1053/j.ajkd.2008.12.042.

71. Das SK, Mannan M, Faruque ASG, Ahmed T, McIntyre HD, Al Mamun A. Effect of birth weight on adulthood renal function: A bias-adjusted meta-analytic approach. *Nephrology*. 2016;21(7):547-565. doi:10.1111/nep.12732.

72. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer—experiences of the son. *Int J Epidemiol*. 2010;39(6):1605-1618. doi:10.1093/ije/dyq120.

73. Xue F, Michels KB. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. *Lancet Oncol*. 2007;8(12):1088-1100. doi:10.1016/S1470-2045(07)70377-7.

74. Zhou CK, Sutcliffe S, Welsh J, Mackinnon K, Kuh D, Hardy R, Cook MB. Is birthweight associated with total and aggressive/lethal prostate cancer risks? A systematic review and meta-analysis. *Br J Cancer*. 2016;114(7):839-848. doi:10.1038/bjc.2016.38.

75. Hjalgrim LL, Westergaard T, Rostgaard K, Schmiegelow K, Melbye M, Hjalgrim H, Engels EA. Birth weight as a risk factor for childhood leukemia: a meta-analysis of 18 epidemiologic studies. *Am J Epidemiol*. 2003;158(8):724-735. http://www.ncbi.nlm.nih.gov/pubmed/14561661. Accessed April 20, 2018.

76. Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, Kajantie E, Osler M, Morley R, Jokela M, Painter RC, Sundh V, Jacobsen GW, Eriksson JG, Sørensen TIA, Bracken MB. Birthweight and mortality in adulthood: a systematic review and meta-analysis. *Int J Epidemiol*. 2011;40(3):647-661. doi:10.1093/ije/dyq267.

77. Eriksson JG, Ylihärsilä H, Forsén T, Osmond C, Barker DJP. Exercise protects against glucose intolerance in individuals with a small body size at birth. *Prev Med (Baltim)*. 2004;39(1):164-167.

doi:10.1016/j.ypmed.2004.01.035.

78. Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen M, Barker DJP, Eriksson JG. Prenatal and childhood growth and leisure time physical activity in adult life. *Eur J Public Health*. 2011;21(6):719-724. doi:10.1093/eurpub/ckq176.
79. Elhakeem A, Cooper R, Bann D, Kuh D, Hardy R. Birth Weight, School Sports Ability, and Adulthood Leisure-Time Physical Activity. *Med Sci Sports Exerc*. 2017;49(1):64-70. doi:10.1249/MSS.0000000000001077.
80. Laaksonen DE, Lakka H-M, Lynch J, Lakka TA, Niskanen L, Rauramaa R, Salonen JT, Kauhanen J. Cardiorespiratory fitness and vigorous leisure-time physical activity modify the association of small size at birth with the metabolic syndrome. *Diabetes Care*. 2003;26(7):2156-2164. http://www.ncbi.nlm.nih.gov/pubmed/12832329. Accessed April 18, 2018.
81. Andersen LG, Ängquist L, Gamborg M, Byberg L, Bengtsson C, Canoy D, Eriksson JG, Eriksson M, Järvelin M-R, Lissner L, Nilsen TI, Osler M, Overvad K, Rasmussen F, Salonen MK, Schack-Nielsen L, Tammelin TH, Tuomainen T-P, Sørensen TIA, et al. Birth Weight in Relation to Leisure Time Physical Activity in Adolescence and Adulthood: Meta-Analysis of Results from 13 Nordic Cohorts. Hernandez A V., ed. *PLoS One*. 2009;4(12):e8192. doi:10.1371/journal.pone.0008192.
82. Pitcher JB, Robertson AL, Cockington RA, Moore VM. Prenatal Growth and Early Postnatal Influences on Adult Motor Cortical Excitability. *Pediatrics*. 2009;124(1):e128-e136. doi:10.1542/peds.2008-1638.
83. Inskip HM, Godfrey KM, Martin HJ, Simmonds SJ, Cooper C, Sayer AA, Southampton Women's Survey Study Group SWSS. Size at birth and its relation to muscle strength in young adult women. *J Intern Med*. 2007;262(3):368-374. doi:10.1111/j.1365-2796.2007.01812.x.
84. Ridgway CL, Sharp SJ, Derom C, Beunen G, Fagard R, Vlietinck R, Ekelund U, Loos RJF. The Contribution of Prenatal Environment and Genetic Factors to the Association between Birth Weight and Adult Grip Strength. Ruiz J, ed. *PLoS One*. 2011;6(3):e17955. doi:10.1371/journal.pone.0017955.
85. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: from the 1982 Pelotas (Brazil) birth cohort. *Nutrition*. 2016;32(2):228-235. doi:10.1016/j.nut.2015.08.014.
86. Kuh D, Bassey J, Hardy R, Aihie Sayer A, Wadsworth M, Cooper C. Birth weight, childhood size, and muscle strength in adult life: evidence from a birth cohort study. *Am J Epidemiol*. 2002;156(7):627-633. http://www.ncbi.nlm.nih.gov/pubmed/12244031. Accessed May 24, 2017.
87. Sayer AA, Syddall H, O'Dell SD, Chen X-H, Briggs PJ, Briggs R, Day INM, Cooper C. Polymorphism of the IGF2 gene, birth weight and grip strength in adult men. *Age Ageing*. 2002;31(6):468-470. http://www.ncbi.nlm.nih.gov/pubmed/12446294. Accessed April 19, 2018.
88. Ylihärsilä H, Kajantie E, Osmond C, Forsén T, Barker DJP, Eriksson JG. Birth size, adult body composition and muscle strength in later life. *Int J Obes (Lond)*. 2007;31(9):1392-1399. doi:10.1038/sj.ijo.0803612.
89. Nahhas RW, Choh AC, Lee M, Chumlea WMC, Duren DL, Siervogel RM, Sherwood RJ, Towne B, Czerwinski SA. Bayesian longitudinal plateau

model of adult grip strength. *Am J Hum Biol*. 2010;22(5):648-656. doi:10.1002/ajhb.21057.

90. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer AA, Baird J. Birth weight and muscle strength: a systematic review and meta-analysis. *J Nutr Health Aging*. 2012;16(7):609-615. http://www.ncbi.nlm.nih.gov/pubmed/22836701. Accessed March 24, 2017.
91. Bleker LS, de Rooij SR, Painter RC, van der Velde N, Roseboom TJ. Prenatal Undernutrition and Physical Function and Frailty at the Age of 68 Years: The Dutch Famine Birth Cohort Study. *J Gerontol A Biol Sci Med Sci*. 2016;71(10):1306-1314. doi:10.1093/gerona/glw081.
92. Young ACM, Glaser K, Spector TD, Steves CJ. The Identification of Hereditary and Environmental Determinants of Frailty in a Cohort of UK Twins. *Twin Res Hum Genet*. 2016;19(06):600-609. doi:10.1017/thg.2016.72.
93. Rosenfeld RG. Insulin-like Growth Factors and the Basis of Growth. *N Engl J Med*. 2003;349(23):2184-2186. doi:10.1056/NEJMp038156.
94. Rolland-Cachera MF, Deheeger M, Bellisle F, Sempé M, Guilloud-Bataille M, Patois E. Adiposity rebound in children: a simple indicator for predicting obesity. *Am J Clin Nutr*. 1984;39(1):129-135. http://www.ncbi.nlm.nih.gov/pubmed/6691287. Accessed June 9, 2017.
95. Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJP. Early adiposity rebound in childhood and risk of Type 2 diabetes in adult life. *Diabetologia*. 2003;46(2):190-194. doi:10.1007/s00125-002-1012-5.
96. Eriksson JG, Forsen TJ, Kajantie E, Osmond C, Barker DJP. Childhood Growth and Hypertension in Later Life. *Hypertension*. 2007;49(6):1415-1421. doi:10.1161/HYPERTENSIONAHA.106.085597.
97. Osmond C, Kajantie E, Forsen TJ, Eriksson JG, Barker DJP. Infant Growth and Stroke in Adult Life: The Helsinki Birth Cohort Study. *Stroke*. 2007;38(2):264-270. doi:10.1161/01.STR.0000254471.72186.03.
98. Halldorsson TI, Gunnarsdottir I, Birgisdottir BE, Gudnason V, Aspelund T, Thorsdottir I. Childhood Growth and Adult Hypertension in a Population of High Birth Weight. *Hypertension*. 2011;58(1):8-15. doi:10.1161/HYPERTENSIONAHA.111.170985.
99. Fall CHD, Sachdev HS, Osmond C, Lakshmy R, Biswas SD, Prabhakaran D, Tandon N, Ramji S, Reddy KS, Barker DJP, Bhargava SK, New Delhi Birth Cohort. Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of BMI gain during infancy: Data from the New Delhi Birth Cohort. *Diabetes Care*. 2008;31(12):2349-2356. doi:10.2337/dc08-0911.
100. Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen M, Barker DJP, Eriksson JG. Role of childhood growth on the risk of metabolic syndrome in obese men and women. *Diabetes Metab*. 2009;35(35):94-100. doi:10.1016/j.diabet.2008.08.008.
101. Bhargava SK, Sachdev HS, Fall CHD, Osmond C, Lakshmy R, Barker DJP, Biswas SKD, Ramji S, Prabhakaran D, Reddy KS. Relation of Serial Changes in Childhood Body-Mass Index to Impaired Glucose Tolerance in Young Adulthood. *N Engl J Med*. 2004;350(9):865-875. doi:10.1056/NEJMoa035698.
102. Mikkola TM, von Bonsdorff MB, Osmond C, Salonen MK, Kajantie E, Cooper C, Välimäki MJ, Eriksson JG. Childhood growth predicts higher

bone mass and greater bone area in early old age: findings among a subgroup of women from the Helsinki Birth Cohort Study. *Osteoporos Int*. 2017;28(9):2717-2722. doi:10.1007/s00198-017-4048-6.

103. Kuh D, Wills AK, Shah I, Prentice A, Hardy R, Adams JE, Ward K, Cooper C, National Survey for Health and Development (NSHD) Scientific and Data Collection Team. Growth From Birth to Adulthood and Bone Phenotype in Early Old Age: A British Birth Cohort Study. *J Bone Miner Res*. 2014;29(1):123-133. doi:10.1002/jbmr.2008.
104. Orfei L, Strachan DP, Rudnicka AR, Wadsworth MEJ. Early influences on adult lung function in two national British cohorts. *Arch Dis Child*. 2008;93(7):570-574. doi:10.1136/adc.2006.112201.
105. Loret de Mola C, Quevedo L de A, Pinheiro RT, Gonçalves H, Gigante DP, Motta JVDS, Barros FC, Horta BL. The Effect of Fetal and Childhood Growth over Depression in Early Adulthood in a Southern Brazilian Birth Cohort. *PLoS One*. 2015;10(10):e0140621. doi:10.1371/journal.pone.0140621.
106. von Bonsdorff MB, Törmäkangas T, Rantanen T, Salonen MK, Osmond C, Kajantie E, Eriksson JG. Early life body mass trajectories and mortality in older age: Findings from the Helsinki Birth Cohort Study. *Ann Med*. 2015;47(1):34-39. doi:10.3109/07853890.2014.963664.
107. Kuzawa CW, McDade TW, Adair LS, Lee N. Rapid weight gain after birth predicts life history and reproductive strategy in Filipino males. *Proc Natl Acad Sci*. 2010;107(39):16800-16805. doi:10.1073/pnas.1006008107.
108. Sayer AA, Syddall HE, Gilbody HJ, Dennison EM, Cooper C. Does sarcopenia originate in early life? Findings from the Hertfordshire cohort study. *J Gerontol A Biol Sci Med Sci*. 2004;59(9):M930-4. http://www.ncbi.nlm.nih.gov/pubmed/15472158. Accessed March 13, 2017.
109. Kuh, Hardy, Butterworth S, Okell L, Wadsworth M, Cooper C, Aihie Sayer A. Developmental origins of midlife grip strength: findings from a birth cohort study. *J Gerontol A Biol Sci Med Sci*. 2006;61(7):702-706. http://www.ncbi.nlm.nih.gov/pubmed/16870632. Accessed March 11, 2017.
110. Martin HJ, Syddall HE, Dennison EM, Cooper C, Aihie Sayer A. Physical Performance and Physical Activity in Older People: Are Developmental Influences Important? *Gerontology*. 2009;55(2):186-193. doi:10.1159/000174823.
111. von Bonsdorff MB, Rantanen T, Sipila S, Salonen MK, Kajantie E, Osmond C, Barker DJP, Eriksson JG. Birth Size and Childhood Growth as Determinants of Physical Functioning in Older Age: The Helsinki Birth Cohort Study. *Am J Epidemiol*. 2011;174(12):1336-1344. doi:10.1093/aje/kwr270.
112. Kuh, Hardy R, Butterworth S, Okell L, Richards M, Wadsworth M, Cooper C, Sayer AA. Developmental Origins of Midlife Physical Performance: Evidence from a British Birth Cohort. *Am J Epidemiol*. 2006;164(2):110-121. doi:10.1093/aje/kwj193.
113. Eriksson JG, Osmond C, Perälä M-M, Salonen MK, Simonen M, Pohjolainen P, Kajantie E, Rantanen T, von Bonsdorff MB. Prenatal and childhood growth and physical performance in old age--findings from the Helsinki Birth Cohort Study 1934-1944. *Age (Dordr)*. 2015;37(6):108. doi:10.1007/s11357-015-9846-1.
114. Chrousos GP. Stress and disorders of the stress system. *Nat Rev*

Endocrinol. 2009;5(7):374-381. doi:10.1038/nrendo.2009.106.

115. Matthews SG. Antenatal glucocorticoids and programming of the developing CNS. *Pediatr Res*. 2000;47(3):291-300. http://www.ncbi.nlm.nih.gov/pubmed/10709726. Accessed August 31, 2018.
116. Mueller BR, Bale TL. Sex-Specific Programming of Offspring Emotionality after Stress Early in Pregnancy. *J Neurosci*. 2008;28(36):9055-9065. doi:10.1523/JNEUROSCI.1424-08.2008.
117. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009;10(6):434-445. doi:10.1038/nrn2639.
118. Strüber N, Strüber D, Roth G. Impact of early adversity on glucocorticoid regulation and later mental disorders. *Neurosci Biobehav Rev*. 2014;38:17-37. doi:10.1016/j.neubiorev.2013.10.015.
119. LaPrairie JL, Heim CM, Nemeroff CB. The neuroendocrine effects of early life trauma. In: Lanius RA, Vermetten E, Pain C, eds. *The Impact of Early Life Trauma on Health and Disease*. Cambridge: Cambridge University Press; 2010:157-165. doi:10.1017/CBO9780511777042.019.
120. Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Association Between Prenatal Exposure to Bacterial Infection and Risk of Schizophrenia. *Schizophr Bull*. 2009;35(3):631-637. doi:10.1093/schbul/sbn121.
121. Carpenter LL, Carvalho JP, Tyrka AR, Wier LM, Mello AF, Mello MF, Anderson GM, Wilkinson CW, Price LH. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biol Psychiatry*. 2007;62(10):1080-1087. doi:10.1016/j.biopsych.2007.05.002.
122. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The Long-Term Health Consequences of Child Physical Abuse, Emotional Abuse, and Neglect: A Systematic Review and Meta-Analysis. Tomlinson M, ed. *PLoS Med*. 2012;9(11):e1001349. doi:10.1371/journal.pmed.1001349.
123. Mack KY. Childhood Family Disruptions and Adult Well-Being: The Differential Effects of Divorce and Parental Death. *Death Stud*. 2001;25(5):419-443. doi:10.1080/074811801750257527.
124. Maier EH, Lachman ME. Consequences of early parental loss and separation for health and well-being in midlife. *Int J Behav Dev*. 2000;24(2):183-189. doi:10.1080/016502500383304.
125. Pesonen A-K, Raikkonen K, Heinonen K, Kajantie E, Forsen T, Eriksson JG. Depressive Symptoms in Adults Separated from Their Parents as Children: A Natural Experiment during World War II. *Am J Epidemiol*. 2007;166(10):1126-1133. doi:10.1093/aje/kwm254.
126. Rusby JSM, Tasker F. Long-term effects of the British evacuation of children during World War 2 on their adult mental health. *Aging Ment Health*. 2009;13(3):391-404. doi:10.1080/13607860902867750.
127. Räikkönen K, Lahti M, Heinonen K, Pesonen A-K, Wahlbeck K, Kajantie E, Osmond C, Barker DJP, Eriksson JG. Risk of severe mental disorders in adults separated temporarily from their parents in childhood: The Helsinki birth cohort study. *J Psychiatr Res*. 2011;45(3):332-338. doi:10.1016/j.jpsychires.2010.07.003.
128. Lahti M, Pesonen A-K, Räikkönen K, Heinonen K, Wahlbeck K, Kajantie E, Osmond C, Barker DJP, Eriksson JG. Temporary Separation from Parents in Early Childhood and Serious Personality Disorders in Adult Life. *J Pers Disord*. 2012;26(5):751-762.

doi:10.1521/pedi.2012.26.5.751.

129. Foster D, Davies S, Steele H. The evacuation of British children during World War II: A preliminary investigation into the long-term psychological effects. *Aging Ment Health*. 2003;7(5):398-408. doi:10.1080/1360786031000150711.
130. Afifi TO, Enns MW, Cox BJ, de Graaf R, ten Have M, Sareen J. Child Abuse and Health-Related Quality of Life in Adulthood. *J Nerv Ment Dis*. 2007;195(10):797-804. doi:10.1097/NMD.0b013e3181567fdd.
131. Draper B, Pfaff JJ, Pirkis J, Snowdon J, Lautenschlager NT, Wilson I, Almeida OP, Depression and Early Prevention of Suicide in General Practice Study Group. Long-Term Effects of Childhood Abuse on the Quality of Life and Health of Older People: Results from the Depression and Early Prevention of Suicide in General Practice Project. *J Am Geriatr Soc*. 2008;56(2):262-271. doi:10.1111/j.1532-5415.2007.01537.x.
132. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245-258. http://www.ncbi.nlm.nih.gov/pubmed/9635069. Accessed August 31, 2018.
133. Thomas C, Hypponen E, Power C. Obesity and Type 2 Diabetes Risk in Midadult Life: The Role of Childhood Adversity. *Pediatrics*. 2008;121(5):e1240-e1249. doi:10.1542/peds.2007-2403.
134. Scott KM, Von Korff M, Angermeyer MC, Benjet C, Bruffaerts R, de Girolamo G, Haro JM, Lépine J-P, Ormel J, Posada-Villa J, Tachimori H, Kessler RC. Association of Childhood Adversities and Early-Onset Mental Disorders With Adult-Onset Chronic Physical Conditions. *Arch Gen Psychiatry*. 2011;68(8):838. <
135. Corso PS, Edwards VJ, Fang X, Mercy JA. Health-related quality of life among adults who experienced maltreatment during childhood. *Am J Public Health*. 2008;98(6):1094-1100. doi:10.2105/AJPH.2007.119826.
136. Goodwin RD, Stein MB. Association between childhood trauma and physical disorders among adults in the United States. *Psychol Med*. 2004;34(3):509-520. doi:10.1017/S003329170300134X.
137. Fuller-Thomson E, Brennenstuhl S, Frank J. The association between childhood physical abuse and heart disease in adulthood: Findings from a representative community sample. *Child Abuse Negl*. 2010;34(9):689-698. doi:10.1016/j.chiabu.2010.02.005.
138. Alastalo H, Raikkonen K, Pesonen A-K, Osmond C, Barker DJP, Kajantie E, Heinonen K, Forsen TJ, Eriksson JG. Cardiovascular health of Finnish war evacuees 60 years later. *Ann Med*. 2009;41(1):66-72. doi:10.1080/07853890802301983.
139. Alastalo H, Räikkönen K, Pesonen A-K, Osmond C, Barker DJP, Heinonen K, Kajantie E, Eriksson JG. Cardiovascular Morbidity and Mortality in Finnish Men and Women Separated Temporarily From Their Parents in Childhood—A Life Course Study. *Psychosom Med*. 2012;74(6):583-587. doi:10.1097/PSY.0b013e31825b3d76.
140. Koupil I, Shestov DB, Sparén P, Plavinskaja S, Parfenova N, Vågerö D. Blood pressure, hypertension and mortality from circulatory disease in men and women who survived the siege of Leningrad. *Eur J Epidemiol*. 2007;22(4):223-234. doi:10.1007/s10654-007-9113-6.

141. Alastalo H, Räikkönen K, Pesonen A-K, Osmond C, Barker DJP, Heinonen K, Kajantie E, Eriksson JG. Early life stress and blood pressure levels in late adulthood. *J Hum Hypertens*. 2013;27(2):90-94. doi:10.1038/jhh.2012.6.

142. Agostini A, Rizzello F, Ravegnani G, Gionchetti P, Tambasco R, Straforini G, Ercolani M, Campieri M. Adult Attachment and Early Parental Experiences in Patients With Crohn's Disease. *Psychosomatics*. 2010;51(3):208-215. doi:10.1176/appi.psy.51.3.208.

143. Bradford K, Shih W, Videlock EJ, Presson AP, Naliboff BD, Mayer EA, Chang L. Association Between Early Adverse Life Events and Irritable Bowel Syndrome. *Clin Gastroenterol Hepatol*. 2012;10(4):385-390.e3. doi:10.1016/j.cgh.2011.12.018.

144. dos Santos Gomes C, Pirkle CM, Zunzunegui MV, Taurino Guedes D, Fernandes De Souza Barbosa J, Hwang P, Oliveira Guerra R. Frailty and life course violence: The international mobility in aging study. *Arch Gerontol Geriatr*. 2018;76:26-33. doi:10.1016/j.archger.2018.02.002.

145. Olovnikov AM. [Principle of marginotomy in template synthesis of polynucleotides]. *Dokl Akad Nauk SSSR*. 1971;201(6):1496-1499. http://www.ncbi.nlm.nih.gov/pubmed/5158754. Accessed April 7, 2018.

146. Blackburn EH. Switching and signaling at the telomere. *Cell*. 2001;106(6):661-673. http://www.ncbi.nlm.nih.gov/pubmed/11572773. Accessed November 3, 2017.

147. Okuda K, Bardeguez A, Gardner JP, Rodriguez P, Ganesh V, Kimura M, Skurnick J, Awad G, Aviv A. Telomere Length in the Newborn. *Pediatr Res*. 2002;52(3):377-381. doi:10.1203/00006450-200209000-00012.

148. Aubert G, Baerlocher GM, Vulto I, Poon SS, Lansdorp PM. Collapse of Telomere Homeostasis in Hematopoietic Cells Caused by Heterozygous Mutations in Telomerase Genes. Barsh GS, ed. *PLoS Genet*. 2012;8(5):e1002696. doi:10.1371/journal.pgen.1002696.

149. Sidorov I, Kimura M, Yashin A, Aviv A. Leukocyte telomere dynamics and human hematopoietic stem cell kinetics during somatic growth. *Exp Hematol*. 2009;37(4):514-524. doi:10.1016/j.exphem.2008.11.009.

150. Frenck RW, Blackburn EH, Shannon KM. The rate of telomere sequence loss in human leukocytes varies with age. *Proc Natl Acad Sci U S A*. 1998;95(10):5607-5610. http://www.ncbi.nlm.nih.gov/pubmed/9576930. Accessed April 8, 2018.

151. Benetos A, Kark JD, Susser E, Kimura M, Sinnreich R, Chen W, Steenstrup T, Christensen K, Herbig U, von Bornemann Hjelmborg J, Srinivasan SR, Berenson GS, Labat C, Aviv A. Tracking and fixed ranking of leukocyte telomere length across the adult life course. *Aging Cell*. 2013;12(4):615-621. doi:10.1111/acel.12086.

152. Nordfjäll K, Svenson U, Norrback K-F, Adolfsson R, Lenner P, Roos G. The individual blood cell telomere attrition rate is telomere length dependent. *PLoS Genet*. 2009;5(2):e1000375. doi:10.1371/journal.pgen.1000375.

153. Gardner M, Bann D, Wiley L, Cooper R, Hardy R, Nitsch D, Martin-Ruiz C, Shiels P, Sayer AA, Barbieri M, Bekaert S, Bischoff C, Brooks-Wilson A, Chen W, Cooper C, Christensen K, De Meyer T, Deary I, Der G, et al. Gender and telomere length: Systematic review and meta-analysis. *Exp Gerontol*. 2014;51:15-27. doi:10.1016/j.exger.2013.12.004.

154. Aviv A, Chen W, Gardner JP, Kimura M, Brimacombe M, Cao X, Srinivasan SR, Berenson GS. Leukocyte telomere dynamics: longitudinal findings among young adults in the Bogalusa Heart Study. *Am J Epidemiol*. 2009;169(3):323-329. doi:10.1093/aje/kwn338.

155. Daniali L, Benetos A, Susser E, Kark JD, Labat C, Kimura M, Desai K, Granick M, Aviv A. Telomeres shorten at equivalent rates in somatic tissues of adults. *Nat Commun*. 2013;4:1597. doi:10.1038/ncomms2602.

156. Moyzis RK, Buckingham JM, Cram LS, Dani M, Deaven LL, Jones MD, Meyne J, Ratliff RL, Wu JR. A highly conserved repetitive DNA sequence, (TTAGGG)n, present at the telomeres of human chromosomes. *Proc Natl Acad Sci U S A*. 1988;85(18):6622-6626. http://www.ncbi.nlm.nih.gov/pubmed/3413114. Accessed November 9, 2018.

157. Lai T-P, Wright WE, Shay JW. Comparison of telomere length measurement methods. *Philos Trans R Soc B Biol Sci*. 2018;373(1741):20160451. doi:10.1098/rstb.2016.0451.

158. Kimura M, Stone RC, Hunt SC, Skurnick J, Lu X, Cao X, Harley CB, Aviv A. Measurement of telomere length by the Southern blot analysis of terminal restriction fragment lengths. *Nat Protoc*. 2010;5(9):1596-1607. doi:10.1038/nprot.2010.124.

159. Mender I, Shay JW. Telomere Restriction Fragment (TRF) Analysis. *Bio-protocol*. 2015;5(22). http://www.ncbi.nlm.nih.gov/pubmed/27500189. Accessed November 9, 2018.

160. Cawthon RM. Telomere measurement by quantitative PCR. *Nucleic Acids Res*. 2002;30(10):e47. http://www.ncbi.nlm.nih.gov/pubmed/12000852. Accessed July 30, 2017.

161. Cawthon RM. Telomere length measurement by a novel monochrome multiplex quantitative PCR method. *Nucleic Acids Res*. 2009;37(3):e21. doi:10.1093/nar/gkn1027.

162. Calado RT, Young NS. Telomere diseases. *N Engl J Med*. 2009;361(24):2353-2365. doi:10.1056/NEJMra0903373.

163. O'Donnell CJ, Demissie S, Kimura M, Levy D, Gardner JP, White C, D'Agostino RB, Wolf PA, Polak J, Cupples LA, Aviv A. Leukocyte telomere length and carotid artery intimal medial thickness: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2008;28(6):1165-1171. doi:10.1161/ATVBAHA.107.154849.

164. Toupance S, Labat C, Temmar M, Rossignol P, Kimura M, Aviv A, Benetos A. Short Telomeres, but Not Telomere Attrition Rates, Are Associated With Carotid Atherosclerosis. *Hypertens (Dallas, Tex 1979)*. 2017;70(2):420-425. doi:10.1161/HYPERTENSIONAHA.117.09354.

165. Brouilette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, Packard CJ, Samani NJ, West of Scotland Coronary Prevention Study Group. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. *Lancet*. 2007;369(9556):107-114. doi:10.1016/S0140-6736(07)60071-3.

166. Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Walston J, Kimura M, Aviv A. Leukocyte Telomere Length and Cardiovascular Disease in the Cardiovascular Health Study. *Am J Epidemiol*. 2006;165(1):14-21. doi:10.1093/aje/kwj346.

167. Brouilette S, Singh RK, Thompson JR, Goodall AH, Samani NJ. White cell telomere length and risk of premature myocardial infarction. *Arterioscler Thromb Vasc Biol*. 2003;23(5):842-846. doi:10.1161/01.ATV.0000067426.96344.32.

168. Farzaneh-Far R, Cawthon RM, Na B, Browner WS, Schiller NB, Whooley MA. Prognostic value of leukocyte telomere length in patients with stable coronary artery disease: data from the Heart and Soul Study. *Arterioscler Thromb Vasc Biol*. 2008;28(7):1379-1384. doi:10.1161/ATVBAHA.108.167049.

169. Staerk L, Wang B, Lunetta KL, Helm RH, Ko D, Sherer JA, Ellinor PT, Lubitz SA, McManus DD, Vasan RS, Benjamin EJ, Trinquart L. Association Between Leukocyte Telomere Length and the Risk of Incident Atrial Fibrillation: The Framingham Heart Study. *J Am Heart Assoc*. 2017;6(11). doi:10.1161/JAHA.117.006541.

170. Adaikalakoteswari A, Balasubramanyam M, Ravikumar R, Deepa R, Mohan V. Association of telomere shortening with impaired glucose tolerance and diabetic macroangiopathy. *Atherosclerosis*. 2007;195(1):83-89. doi:10.1016/j.atherosclerosis.2006.12.003.

171. Sampson MJ, Winterbone MS, Hughes JC, Dozio N, Hughes DA. Monocyte telomere shortening and oxidative DNA damage in type 2 diabetes. *Diabetes Care*. 2006;29(2):283-289. http://www.ncbi.nlm.nih.gov/pubmed/16443874. Accessed November 3, 2017.

172. Zee RYL, Castonguay AJ, Barton NS, Germer S, Martin M. Mean leukocyte telomere length shortening and type 2 diabetes mellitus: a case-control study. *Transl Res*. 2010;155(4):166-169. doi:10.1016/j.trsl.2009.09.012.

173. Willeit P, Raschenberger J, Heydon EE, Tsimikas S, Haun M, Mayr A, Weger S, Witztum JL, Butterworth AS, Willeit J, Kronenberg F, Kiechl S. Leucocyte Telomere Length and Risk of Type 2 Diabetes Mellitus: New Prospective Cohort Study and Literature-Based Meta-Analysis. Lustig AJ, ed. *PLoS One*. 2014;9(11):e112483. doi:10.1371/journal.pone.0112483.

174. Zhao J, Zhu Y, Lin J, Matsuguchi T, Blackburn E, Zhang Y, Cole SA, Best LG, Lee ET, Howard B V. Short leukocyte telomere length predicts risk of diabetes in american indians: the strong heart family study. *Diabetes*. 2014;63(1):354-362. doi:10.2337/db13-0744.

175. You N-CY, Chen BH, Song Y, Lu X, Chen Y, Manson JE, Kang M, Howard B V, Margolis KL, Curb JD, Phillips LS, Stefanick ML, Tinker LF, Liu S. A prospective study of leukocyte telomere length and risk of type 2 diabetes in postmenopausal women. *Diabetes*. 2012;61(11):2998-3004. doi:10.2337/db12-0241.

176. Njajou OT, Cawthon RM, Blackburn EH, Harris TB, Li R, Sanders JL, Newman AB, Nalls M, Cummings SR, Hsueh W-C. Shorter telomeres are associated with obesity and weight gain in the elderly. *Int J Obes (Lond)*. 2012;36(9):1176-1179. doi:10.1038/ijo.2011.196.

177. Ma H, Zhou Z, Wei S, Liu Z, Pooley KA, Dunning AM, Svenson U, Roos G, Hosgood HD, Shen M, Wei Q. Shortened Telomere Length Is Associated with Increased Risk of Cancer: A Meta-Analysis. Toland AE, ed. *PLoS One*. 2011;6(6):e20466. doi:10.1371/journal.pone.0020466.

178. Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA. The association of telomere length and cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2011;20(6):1238-1250. doi:10.1158/1055-9965.EPI-11-0005.

179. Burke LS, Hyland PL, Pfeiffer RM, Prescott J, Wheeler W, Mirabello L, Savage SA, Burdette L, Yeager M, Chanock S, De Vivo I, Tucker MA, Goldstein AM, Yang XR. Telomere Length and the Risk of Cutaneous Malignant Melanoma in Melanoma-Prone Families with and without CDKN2A Mutations. Soyer HP, ed. *PLoS One*. 2013;8(8):e71121. doi:10.1371/journal.pone.0071121.
180. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet*. 2003;361(9355):393-395. doi:10.1016/S0140-6736(03)12384-7.
181. Rode L, Nordestgaard BG, Bojesen SE. Peripheral Blood Leukocyte Telomere Length and Mortality Among 64 637 Individuals From the General Population. *JNCI J Natl Cancer Inst*. 2015;107(6):djv074. doi:10.1093/jnci/djv074.
182. Needham BL, Rehkopf D, Adler N, Gregorich S, Lin J, Blackburn EH, Epel ES. Leukocyte Telomere Length and Mortality in the National Health and Nutrition Examination Survey, 1999–2002. *Epidemiology*. 2015;26(4):528-535. doi:10.1097/EDE.0000000000000299.
183. Martin-Ruiz CM, Gussekloo J, Heemst D, Zglinicki T, Westendorp RGJ. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: a population-based study. *Aging Cell*. 2005;4(6):287-290. doi:10.1111/j.1474-9726.2005.00171.x.
184. Oh H, Wang SC, Prahash A, Sano M, Moravec CS, Taffet GE, Michael LH, Youker KA, Entman ML, Schneider MD. Telomere attrition and Chk2 activation in human heart failure. *Proc Natl Acad Sci*. 2003;100(9):5378-5383. doi:10.1073/pnas.0836098100.
185. Savale L, Chaouat A, Bastuji-Garin S, Marcos E, Boyer L, Maitre B, Sarni M, Housset B, Weitzenblum E, Matrat M, Le Corvoisier P, Rideau D, Boczkowski J, Dubois-Randé J-L, Chouaid C, Adnot S. Shortened Telomeres in Circulating Leukocytes of Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2009;179(7):566-571. c
186. Lee J, Sandford AJ, Connett JE, Yan J, Mui T, Li Y, Daley D, Anthonisen NR, Brooks-Wilson A, Man SFP, Sin DD. The Relationship between Telomere Length and Mortality in Chronic Obstructive Pulmonary Disease (COPD). Taube C, ed. *PLoS One*. 2012;7(4):e35567. doi:10.1371/journal.pone.0035567.
187. O'Sullivan JN, Bronner MP, Brentnall TA, Finley JC, Shen W-T, Emerson S, Emond MJ, Gollahon KA, Moskovitz AH, Crispin DA, Potter JD, Rabinovitch PS. Chromosomal instability in ulcerative colitis is related to telomere shortening. *Nat Genet*. 2002;32(2):280-284. doi:10.1038/ng989.
188. Cottliar A, Palumbo M, Motta G, Barrio S, Crivelli A, Viola M, Gomez JC, Slavutsky I. Telomere length study in celiac disease. *Am J Gastroenterol*. 2003;98(12):2727-2731. doi:10.1111/j.1572-0241.2003.08720.x.
189. Hochstrasser T, Marksteiner J, Humpel C. Telomere length is age-dependent and reduced in monocytes of Alzheimer patients. *Exp Gerontol*. 2012;47(2):160-163. doi:10.1016/j.exger.2011.11.012.
190. Panossian LA, Porter VR, Valenzuela HF, Zhu X, Reback E, Masterman D, Cummings JL, Effros RB. Telomere shortening in T cells correlates with Alzheimer's disease status. *Neurobiol Aging*. 24(1):77-84. http://www.ncbi.nlm.nih.gov/pubmed/12493553. Accessed September 22, 2018.

191. Watfa G, Dragonas C, Brosche T, Dittrich R, Sieber CC, Alecu C, Benetos A, Nzietchueng R. Study of telomere length and different markers of oxidative stress in patients with Parkinson's disease. *J Nutr Health Aging*. 2011;15(4):277-281. http://www.ncbi.nlm.nih.gov/pubmed/21437559. Accessed September 22, 2018.

192. Wu C-H, Hsieh S-C, Li K-J, Lu M-C, Yu C-L. Premature telomere shortening in polymorphonuclear neutrophils from patients with systemic lupus erythematosus is related to the lupus disease activity. *Lupus*. 2007;16(4):265-272. doi:10.1177/0961203307077155.

193. Kurosaka D, Yasuda J, Yoshida K, Yoneda A, Yasuda C, Kingetsu I, Toyokawa Y, Yokoyama T, Saito S, Yamada A. Abnormal telomerase activity and telomere length in T and B cells from patients with systemic lupus erythematosus. *J Rheumatol*. 2006;33(6):1102-1107. http://www.ncbi.nlm.nih.gov/pubmed/16755657. Accessed September 22, 2018.

194. Cherkas LF, Hunkin JL, Kato BS, Richards JB, Gardner JP, Surdulescu GL, Kimura M, Lu X, Spector TD, Aviv A. The Association Between Physical Activity in Leisure Time and Leukocyte Telomere Length. *Arch Intern Med*. 2008;168(2):154. doi:10.1001/archinternmed.2007.39.

195. Shadyab A, LaMonte M, LaCroix A. Leisure-time physical activity and leukocyte telomere length among older women. *Exp Gerontol*. 2017;95:141-147. doi:10.1016/j.exger.2017.05.019.

196. Savela S, Saijonmaa O, Strandberg TE, Koistinen P, Strandberg AY, Tilvis RS, Pitkälä KH, Miettinen TA, Fyhrquist F. Physical activity in midlife and telomere length measured in old age. *Exp Gerontol*. 2013;48(1):81-84. doi:10.1016/j.exger.2012.02.003.

197. Gardner MP, Martin-Ruiz C, Cooper R, Hardy R, Sayer AA, Cooper C, Deary IJ, Gallacher J, Harris SE, Shiels PG, Starr JM, Kuh D, von Zglinicki T, Ben-Shlomo Y, Halcyon study team. Telomere Length and Physical Performance at Older Ages: An Individual Participant Meta-Analysis. Vina J, ed. *PLoS One*. 2013;8(7):e69526. doi:10.1371/journal.pone.0069526.

198. Woo J, Yu R, Tang N, Leung J. Telomere length is associated with decline in grip strength in older persons aged 65 years and over. *Age (Omaha)*. 2014;36(5):9711. doi:10.1007/s11357-014-9711-7.

199. Williams DM, Buxton JL, Kantomaa MT, Tammelin TH, Blakemore AIF, Järvelin M-R. Associations of Leukocyte Telomere Length With Aerobic and Muscular Fitness in Young Adults. *Am J Epidemiol*. 2017;185(7):1-9. doi:10.1093/aje/kww123.

200. Shadyab A, LaMonte M, LaCroix A. Association of Accelerometer-Measured Physical Activity With Leukocyte Telomere Length Among Older Women. *Journals Gerontol Ser A*. 2017;72(11):1532-1537. doi:10.1093/gerona/glx037.

201. Brault ME, Ohayon SM, Kwan R, Bergman H, Eisenberg MJ, Boivin J-F, Morin J-F, Langlois Y, Autexier C, Afilalo J. Telomere Length and the Clinical Phenotype of Frailty in Older Adults Undergoing Cardiac Surgery. *J Am Geriatr Soc*. 2014;62(11):2205-2207. doi:10.1111/jgs.13076.

202. Yu R, Tang N, Leung J, Woo J. Telomere length is not associated with frailty in older Chinese elderly: Cross-sectional and longitudinal analysis. *Mech Ageing Dev*. 2015;152:74-79. doi:10.1016/j.mad.2015.10.002.

203. Arts MHL, Collard RM, Comijs HC, de Jonge L, Penninx BWJH, Naarding P, Kok RM, Oude Voshaar RC. Leucocyte telomere length is no molecular marker of physical frailty in late-life depression. *Exp Gerontol*. 2018;111:229-234. doi:10.1016/j.exger.2018.07.016.

204. Woo J, Tang NLS, Suen E, Leung JCS, Leung PC. Telomeres and frailty. *Mech Ageing Dev*. 2008;129(11):642-648. doi:10.1016/j.mad.2008.08.003.

205. Saum K-U, Dieffenbach AK, Müezzinler A, Müller H, Holleczek B, Stegmaier C, Butterbach K, Schick M, Canzian F, Stammer H, Boukamp P, Hauer K, Brenner H. Frailty and telomere length: Cross-sectional analysis in 3537 older adults from the ESTHER cohort. *Exp Gerontol*. 2014;58:250-255. doi:10.1016/j.exger.2014.08.009.

206. Breitling LP, Saum K-U, Perna L, Schöttker B, Holleczek B, Brenner H. Frailty is associated with the epigenetic clock but not with telomere length in a German cohort. *Clin Epigenetics*. 2016;8:21. doi:10.1186/s13148-016-0186-5.

207. Collerton J, Martin-Ruiz C, Davies K, Hilkens CM, Isaacs J, Kolenda C, Parker C, Dunn M, Catt M, Jagger C, von Zglinicki T, Kirkwood TBL. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the Newcastle 85+ Study. *Mech Ageing Dev*. 2012;133(6):456-466. doi:10.1016/j.mad.2012.05.005.

208. Marzetti E, Lorenzi M, Antocicco M, Bonassi S, Celi M, Mastropaolo S, Settanni S, Valdiglesias V, Landi F, Bernabei R, Onder G. Shorter telomeres in peripheral blood mononuclear cells from older persons with sarcopenia: results from an exploratory study. *Front Aging Neurosci*. 2014;6:233. doi:10.3389/fnagi.2014.00233.

209. Ortiz-Ramírez M, Sánchez-García S, García-Dela Torre P, Reyes-Maldonado E, Sánchez-Arenas R, Rosas-Vargas H. Telomere shortening and frailty in Mexican older adults. *Geriatr Gerontol Int*. 2018;18(8):1286-1292. doi:10.1111/ggi.13463.

210. Dent E, Hoogendijk EO, Moldovan M. Frailty index from routine laboratory measurements correlates with leukocyte telomere length. *Geriatr Gerontol Int*. 2018;18(4):654-655. doi:10.1111/ggi.13257.

211. Teubel I, Elchinova E, Roura S, Fernández MA, Gálvez-Montón C, Moliner P, de Antonio M, Lupón J, Bayés-Genís A. Telomere attrition in heart failure: a flow-FISH longitudinal analysis of circulating monocytes. *J Transl Med*. 2018;16(1):35. doi:10.1186/s12967-018-1412-z.

212. Révész D, Verhoeven JE, Picard M, Lin J, Sidney S, Epel ES, Penninx BWJH, Puterman E. Associations Between Cellular Aging Markers and Metabolic Syndrome: Findings From the CARDIA Study. *J Clin Endocrinol Metab*. 2018;103(1):148-157. doi:10.1210/jc.2017-01625.

213. Wulaningsih W, Kuh D, Wong A, Hardy R. Adiposity, Telomere Length, and Telomere Attrition in Midlife: the 1946 British Birth Cohort. *Journals Gerontol Ser A*. 2018;73(7):966-972. doi:10.1093/gerona/glx151.

214. Gardner JP, Li S, Srinivasan SR, Chen W, Kimura M, Lu X, Berenson GS, Aviv A. Rise in Insulin Resistance Is Associated With Escalated Telomere Attrition. *Circulation*. 2005;111(17):2171-2177. doi:10.1161/01.CIR.0000163550.70487.0B.

215. Chang S-C, Crous-Bou M, Prescott J, Rosner B, Simon NM, Wang W, De Vivo I, Okereke OI. Prospective association of depression and phobic

anxiety with changes in telomere lengths over 11 years. *Depress Anxiety*. 2018;35(5):431-439. doi:10.1002/da.22732.

216. Verhoeven JE, van Oppen P, Révész D, Wolkowitz OM, Penninx BWJH. Depressive and Anxiety Disorders Showing Robust, but Non-Dynamic, 6-Year Longitudinal Association With Short Leukocyte Telomere Length. *Am J Psychiatry*. 2016;173(6):617-624. doi:10.1176/appi.ajp.2015.15070887.
217. Córdoba-Lanús E, Cazorla-Rivero S, Espinoza-Jiménez A, de-Torres JP, Pajares MJ, Aguirre-Jaime A, Celli B, Casanova C. Telomere shortening and accelerated aging in COPD: findings from the BODE cohort. *Respir Res*. 2017;18(1):59. doi:10.1186/s12931-017-0547-4.
218. Staffaroni AM, Tosun D, Lin J, Elahi FM, Casaletto KB, Wynn MJ, Patel N, Neuhaus J, Walters SM, Epel ES, Blackburn EH, Kramer JH. Telomere attrition is associated with declines in medial temporal lobe volume and white matter microstructure in functionally independent older adults. *Neurobiol Aging*. 2018;69:68-75. doi:10.1016/j.neurobiolaging.2018.04.021.
219. Cohen-Manheim I, Doniger GM, Sinnreich R, Simon ES, Pinchas R, Aviv A, Kark JD. Increased attrition of leukocyte telomere length in young adults is associated with poorer cognitive function in midlife. *Eur J Epidemiol*. 2016;31(2):147-157. doi:10.1007/s10654-015-0051-4.
220. Bendix L, Thinggaard M, Fenger M, Kolvraa S, Avlund K, Linneberg A, Osler M. Longitudinal Changes in Leukocyte Telomere Length and Mortality in Humans. *Journals Gerontol Ser A*. 2014;69A(2):231-239. doi:10.1093/gerona/glt153.
221. Baylis D, Ntani G, Edwards MH, Syddall HE, Bartlett DB, Dennison EM, Martin-Ruiz C, von Zglinicki T, Kuh D, Lord JM, Aihie Sayer A, Cooper C. Inflammation, telomere length, and grip strength: a 10-year longitudinal study. *Calcif Tissue Int*. 2014;95(1):54-63. doi:10.1007/s00223-014-9862-7.
222. Harris SE, Marioni RE, Martin-Ruiz C, Pattie A, Gow AJ, Cox SR, Corley J, von Zglinicki T, Starr JM, Deary IJ. Longitudinal telomere length shortening and cognitive and physical decline in later life: The Lothian Birth Cohorts 1936 and 1921. *Mech Ageing Dev*. 2016;154:43-48. doi:10.1016/j.mad.2016.02.004.
223. American Medical Association white paper on elderly health. Report of the Council on Scientific Affairs. *Arch Intern Med*. 1990;150(12):2459-2472. http://www.ncbi.nlm.nih.gov/pubmed/2288622. Accessed October 19, 2018.
224. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, Cesari M, Chumlea WC, Doehner W, Evans J, Fried LP, Guralnik JM, Katz PR, Malmstrom TK, McCarter RJ, Gutierrez Robledo LM, Rockwood K, von Haehling S, Vandewoude MF, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397. doi:10.1016/j.jamda.2013.03.022.
225. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the center for epidemiological studies depression (CES-D) scale. *J Clin Psychol*. 1986;42(1):28-33. doi:10.1002/1097-4679(198601)42:1<28::AID-JCLP2270420104>3.0.CO;2-T.
226. Taylor HL, Jacobs DR, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis*. 1978;31(12):741-755. doi:10.1016/0021-9681(78)90058-9.
227. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a

proxy measure of aging. *ScientificWorldJournal*. 2001;1:323-336. doi:10.1100/tsw.2001.58.

228. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8(1):24. doi:10.1186/1471-2318-8-24.
229. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review. *J Am Geriatr Soc*. 2012;60(8):1487-1492. doi:10.1111/j.1532-5415.2012.04054.x.
230. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc*. 2015;16(11):940-945. doi:10.1016/j.jamda.2015.06.025.
231. Kojima G, Taniguchi Y, Iliffe S, Walters K. Frailty as a Predictor of Alzheimer Disease, Vascular Dementia, and All Dementia Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc*. 2016;17(10):881-888. doi:10.1016/j.jamda.2016.05.013.
232. Vermeiren S, Vella-Azzopardi R, Beckwée D, Habbig A-K, Scafoglieri A, Jansen B, Bautmans I, Bautmans I, Verté D, Beyer I, Petrovic M, De Donder L, Kardol T, Rossi G, Clarys P, Scafoglieri A, Cattrysse E, de Hert P, Jansen B. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. *J Am Med Dir Assoc*. 2016;17(12):1163.e1-1163.e17. doi:10.1016/j.jamda.2016.09.010.
233. Kojima G. Frailty Defined by FRAIL Scale as a Predictor of Mortality: A Systematic Review and Meta-analysis. *J Am Med Dir Assoc*. 2018;19(6):480-483. doi:10.1016/j.jamda.2018.04.006.
234. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. *Age Ageing*. 2018;47(2):193-200. doi:10.1093/ageing/afx162.
235. Alvarado BE, Zunzunegui M-V, Béland F, Bamvita J-M. Life course social and health conditions linked to frailty in Latin American older men and women. *J Gerontol A Biol Sci Med Sci*. 2008;63(12):1399-1406. http://www.ncbi.nlm.nih.gov/pubmed/19126855. Accessed March 11, 2017.
236. Herr M, Robine J-M, Aegerter P, Arvieu J-J, Ankri J. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. *Ann Epidemiol*. 2015;25(9):674-680.e1. doi:10.1016/j.annepidem.2015.05.006.
237. Gale CR, Booth T, Starr JM, Deary IJ. Intelligence and socioeconomic position in childhood in relation to frailty and cumulative allostatic load in later life: the Lothian Birth Cohort 1936. *J Epidemiol Community Health*. 2016;70(6):576-582. doi:10.1136/jech-2015-205789.
238. Myers V, Drory Y, Goldbourt U, Gerber Y. Multilevel socioeconomic status and incidence of frailty post myocardial infarction. *Int J Cardiol*. 2014;170(3):338-343. doi:10.1016/j.ijcard.2013.11.009.
239. Hoogendijk EO, van Hout HPJ, Heymans MW, van der Horst HE, Frijters DHM, Broese van Groenou MI, Deeg DJH, Huisman M. Explaining the association between educational level and frailty in older adults: results from a 13-year longitudinal study in the Netherlands. *Ann Epidemiol*. 2014;24(7):538-544.e2. doi:10.1016/j.annepidem.2014.05.002.
240. Talegawkar SA, Bandinelli S, Bandeen-Roche K, Chen P, Milaneschi Y,

Tanaka T, Semba RD, Guralnik JM, Ferrucci L. A Higher Adherence to a Mediterranean-Style Diet Is Inversely Associated with the Development of Frailty in Community-Dwelling Elderly Men and Women. *J Nutr*. 2012;142(12):2161-2166. doi:10.3945/jn.112.165498.

241. Walker KA, Walston J, Gottesman RF, Kucharska-Newton A, Palta P, Windham BG. Midlife Systemic Inflammation Is Associated With Frailty in Later Life: The ARIC Study. *Journals Gerontol Ser A*. March 2018. doi:10.1093/gerona/gly045.
242. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med*. 2007;167(7):635-641. doi:10.1001/archinte.167.7.635.
243. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, Gottdiener J, Fried LP, Cardiovascular Health Study. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med*. 2002;162(20):2333-2341. http://www.ncbi.nlm.nih.gov/pubmed/12418947. Accessed September 18, 2018.
244. Kojima G, Avgerinou C, Iliffe S, Walters K. Adherence to Mediterranean Diet Reduces Incident Frailty Risk: Systematic Review and Meta-Analysis. *J Am Geriatr Soc*. 2018;66(4):783-788. doi:10.1111/jgs.15251.
245. Strandberg AY, Trygg T, Pitkälä KH, Strandberg TE. Alcohol consumption in midlife and old age and risk of frailty. *Age Ageing*. 2018;47(2):248-254. doi:10.1093/ageing/afx165.
246. Medzhitov R, Janeway C. Innate Immunity. Mackay IR, Rosen FS, eds. *N Engl J Med*. 2000;343(5):338-344. doi:10.1056/NEJM200008033430506.
247. Bellumkonda L, Tyrrell D, Hummel SL, Goldstein DR. Pathophysiology of heart failure and frailty: a common inflammatory origin? *Aging Cell*. 2017;16(3):444-450. doi:10.1111/acel.12581.
248. Fougère B, Boulanger E, Nourhashémi F, Guyonnet S, Cesari M. Chronic Inflammation: Accelerator of Biological Aging. *Journals Gerontol Ser A Biol Sci Med Sci*. 2016;72(9):glw240. doi:10.1093/gerona/glw240.
249. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*. 2018;15(9):505-522. doi:10.1038/s41569-018-0064-2.
250. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel J-P, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M, European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39(4):412-423. doi:10.1093/ageing/afq034.
251. Marty E, Liu Y, Samuel A, Or O, Lane J. A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease. *Bone*. 2017;105:276-286. doi:10.1016/j.bone.2017.09.008.
252. Bellelli G, Moresco R, Panina-Bordignon P, Arosio B, Gelfi C, Morandi A, Cesari M. Is Delirium the Cognitive Harbinger of Frailty in Older Adults? A Review about the Existing Evidence. *Front Med*. 2017;4:188. doi:10.3389/fmed.2017.00188.
253. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. *lancet Diabetes Endocrinol*. 2018;6(9):743-752. doi:10.1016/S2213-

8587(18)30110-4.

254. Cesari M, Vellas B, Hsu F-C, Newman AB, Doss H, King AC, Manini TM, Church T, Gill TM, Miller ME, Pahor M, LIFE Study Group. A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. *J Gerontol A Biol Sci Med Sci*. 2015;70(2):216-222. doi:10.1093/gerona/glu099.

255. Binder EF, Schechtman KB, Ehsani AA, Steger-May K, Brown M, Sinacore DR, Yarasheski KE, Holloszy JO. Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. *J Am Geriatr Soc*. 2002;50(12):1921-1928. http://www.ncbi.nlm.nih.gov/pubmed/12473001. Accessed September 18, 2018.

256. Giné-Garriga M, Guerra M, Pagès E, Manini TM, Jiménez R, Unnithan VB. The effect of functional circuit training on physical frailty in frail older adults: a randomized controlled trial. *J Aging Phys Act*. 2010;18(4):401-424. http://www.ncbi.nlm.nih.gov/pubmed/20956842. Accessed September 18, 2018.

257. Yamada M, Arai H, Sonoda T, Aoyama T. Community-Based Exercise Program is Cost-Effective by Preventing Care and Disability in Japanese Frail Older Adults. *J Am Med Dir Assoc*. 2012;13(6):507-511. doi:10.1016/j.jamda.2012.04.001.

258. Chan D-CD, Tsou H-H, Yang R-S, Tsauo J-Y, Chen C-Y, Hsiung CA, Kuo KN. A pilot randomized controlled trial to improve geriatric frailty. *BMC Geriatr*. 2012;12(1):58. doi:10.1186/1471-2318-12-58.

259. Kim H, Suzuki T, Kim M, Kojima N, Ota N, Shimotoyodome A, Hase T, Hosoi E, Yoshida H. Effects of exercise and milk fat globule membrane (MFGM) supplementation on body composition, physical function, and hematological parameters in community-dwelling frail Japanese women: a randomized double blind, placebo-controlled, follow-up trial. Buchowski M, ed. *PLoS One*. 2015;10(2):e0116256. doi:10.1371/journal.pone.0116256.

260. Tarazona-Santabalbina FJ, Gómez-Cabrera MC, Pérez-Ros P, Martínez-Arnau FM, Cabo H, Tsaparas K, Salvador-Pascual A, Rodriguez-Mañas L, Viña J. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. *J Am Med Dir Assoc*. 2016;17(5):426-433. doi:10.1016/j.jamda.2016.01.019.

261. Kwon J, Yoshida Y, Yoshida H, Kim H, Suzuki T, Lee Y. Effects of a Combined Physical Training and Nutrition Intervention on Physical Performance and Health-Related Quality of Life in Prefrail Older Women Living in the Community: A Randomized Controlled Trial. *J Am Med Dir Assoc*. 2015;16(3):263.e1-263.e8. doi:10.1016/j.jamda.2014.12.005.

262. Ng TP, Feng L, Nyunt MSZ, Feng L, Niti M, Tan BY, Chan G, Khoo SA, Chan SM, Yap P, Yap KB. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial. *Am J Med*. 2015;128(11):1225-1236.e1. doi:10.1016/j.amjmed.2015.06.017.

263. Borodulin K, Tolonen H, Jousilahti P, Jula A, Juolevi A, Koskinen S, Kuulasmaa K, Laatikainen T, Männistö S, Peltonen M, Perola M, Puska P, Salomaa V, Sundvall J, Virtanen SM, Vartiainen E. Cohort Profile: The National FINRISK Study. *Int J Epidemiol*. 2018;47(3):696-696i. doi:10.1093/ije/dyx239.

264. Central Statistical Office of Finland. *Classification of Socioeconomic Groups: Handbooks 17*. Helsinki, Finland: Central Statistical Office of Finland; 1989.
265. Kavén P. Humanitaarisuuden varjossa: Poliittiset tekijät lastensiirroissa Ruotsiin sotiemme aikana ja niiden jälkeen. 2010.
266. Alastalo H, von Bonsdorff MB, Räikkönen K, Pesonen A-K, Osmond C, Barker DJP, Heinonen K, Kajantie E, Eriksson JG. Early Life Stress and Physical and Psychosocial Functioning in Late Adulthood. Cameron DW, ed. *PLoS One*. 2013;8(7):e69011. doi:10.1371/journal.pone.0069011.
267. Bedogni G, Malavolti M, Severi S, Poli M, Mussi C, Fantuzzi AL, Battistini N. Accuracy of an eight-point tactile-electrode impedance method in the assessment of total body water. *Eur J Clin Nutr*. 2002;56(11):1143-1148. doi:10.1038/sj.ejcn.1601466.
268. Sartorio A, Malavolti M, Agosti F, Marinone PG, Caiti O, Battistini N, Bedogni G. Body water distribution in severe obesity and its assessment from eight-polar bioelectrical impedance analysis. *Eur J Clin Nutr*. 2005;59(2):155-160. doi:10.1038/sj.ejcn.1602049.
269. Beck AT, Steer RA BG. *Manual for the Beck Depression Inventory-II*. San Antonio TX: Psychological Corporation; 1996.
270. Lakka TA, Salonen JT. Intra-person variability of various physical activity assessments in the Kuopio Ischaemic Heart Disease Risk Factor Study. *Int J Epidemiol*. 1992;21(3):467-472. http://www.ncbi.nlm.nih.gov/pubmed/1634307. Accessed April 6, 2017.
271. Kajantie E, Pietilainen KH, Wehkalampi K, Kananen L, Raikkonen K, Rissanen A, Hovi P, Kaprio J, Andersson S, Eriksson JG, Hovatta I. No association between body size at birth and leucocyte telomere length in adult life--evidence from three cohort studies. *Int J Epidemiol*. 2012;41(5):1400-1408. doi:10.1093/ije/dys127.
272. O'Callaghan N, Dhillon V, Thomas P, Fenech M. A quantitative real-time PCR method for absolute telomere length. *Biotechniques*. 2008;44(6):807-809. doi:10.2144/000112761.
273. Royston P. Constructing time-specific reference ranges. *Stat Med*. 1991;10(5):675-690. http://www.ncbi.nlm.nih.gov/pubmed/2068420. Accessed May 28, 2017.
274. Amini SB, Catalano PM, Hirsch V, Mann LI. An analysis of birth weight by gestational age using a computerized perinatal data base, 1975-1992. *Obstet Gynecol*. 1994;83(3):342-352. http://www.ncbi.nlm.nih.gov/pubmed/8127523. Accessed August 28, 2018.
275. Cogswell ME, Yip R. The influence of fetal and maternal factors on the distribution of birthweight. *Semin Perinatol*. 1995;19(3):222-240. http://www.ncbi.nlm.nih.gov/pubmed/7570074. Accessed August 28, 2018.
276. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW V, Eriksson JG, Broekman BFP. Influence of maternal obesity on the long-term health of offspring. *lancet Diabetes Endocrinol*. 2017;5(1):53-64. doi:10.1016/S2213-8587(16)30107-3.
277. Eriksson JG, Sandboge S, Salonen MK, Kajantie E, Osmond C. Long-term consequences of maternal overweight in pregnancy on offspring later health: Findings from the Helsinki Birth Cohort Study. *Ann Med*. 2014;46(6):434-438. doi:10.3109/07853890.2014.919728.

278. Singh AS, Mulder C, Twisk JWR, Van Mechelen W, Chinapaw MJM. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obes Rev*. 2008;9(5):474-488. doi:10.1111/j.1467-789X.2008.00475.x.
279. Brisbois TD, Farmer AP, McCargar LJ. Early markers of adult obesity: a review. *Obes Rev*. 2012;13(4):347-367. doi:10.1111/j.1467-789X.2011.00965.x.
280. Simmonds M, Burch J, Llewellyn A, Griffiths C, Yang H, Owen C, Duffy S, Woolacott N. The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: a systematic review and meta-analysis. *Health Technol Assess*. 2015;19(43):1-336. doi:10.3310/hta19430.
281. Biro FM, Wien M. Childhood obesity and adult morbidities. *Am J Clin Nutr*. 2010;91(5):1499S-1505S. doi:10.3945/ajcn.2010.28701B.
282. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes*. 2011;35(7):891-898. doi:10.1038/ijo.2010.222.
283. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol*. 2018;14(9):513-537. doi:10.1038/s41574-018-0062-9.
284. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, Body Mass Index, and Abdominal Obesity in Older People. *Journals Gerontol Ser A Biol Sci Med Sci*. 2010;65A(4):377-381. doi:10.1093/gerona/glp186.
285. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, Sergi G, Isik AT, Manzato E, Maggi S, Maggio M, Prina AM, Cosco TD, Wu Y-T, Veronese N. Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing Res Rev*. 2016;31:1-8. doi:10.1016/j.arr.2016.08.006.
286. Franceschi C, Campisi J. Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases. *Journals Gerontol Ser A Biol Sci Med Sci*. 2014;69(Suppl 1):S4-S9. doi:10.1093/gerona/glu057.
287. Pesonen A-K, Räikkönen K, Feldt K, Heinonen K, Osmond C, Phillips DIW, Barker DJP, Eriksson JG, Kajantie E. Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. *Psychoneuroendocrinology*. 2010;35(5):758-767. doi:10.1016/j.psyneuen.2009.10.017.
288. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry*. 2008;65(4):409-415. doi:10.1001/archpsyc.65.4.409.
289. Price LH, Kao H-T, Burgers DE, Carpenter LL, Tyrka AR. Telomeres and early-life stress: an overview. *Biol Psychiatry*. 2013;73(1):15-23. doi:10.1016/j.biopsych.2012.06.025.
290. Boersma GJ, Bale TL, Casanello P, Lara HE, Lucion AB, Suchecki D, Tamashiro KL. Long-Term Impact of Early Life Events on Physiology and Behaviour. *J Neuroendocrinol*. 2014;26(9):587-602. doi:10.1111/jne.12153.
291. Fagundes CP, Bennett JM, Derry HM, Kiecolt-Glaser JK. Relationships and Inflammation across the Lifespan: Social Developmental Pathways to Disease. *Soc Personal Psychol Compass*. 2011;5(11):891-903. doi:10.1111/j.1751-9004.2011.00392.x.

292. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science (80-).* 2003;301(5631):386-389. doi:10.1126/science.1083968.

293. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, Pace TWW, Mercer KB, Mayberg HS, Bradley B, Nemeroff CB, Holsboer F, Heim CM, Ressler KJ, Rein T, Binder EB. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci*. 2013;16(1):33-41. doi:10.1038/nn.3275.

294. Bale TL, Epperson CN. Sex differences and stress across the lifespan. *Nat Neurosci*. 2015;18(10):1413-1420. doi:10.1038/nn.4112.

295. Sandman CA, Glynn LM, Davis EP. Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. *J Psychosom Res*. 2013;75(4):327-335. doi:10.1016/j.jpsychores.2013.07.009.

296. Aviv A. Telomeres and human somatic fitness. *J Gerontol A Biol Sci Med Sci*. 2006;61(8):871-873. http://www.ncbi.nlm.nih.gov/pubmed/16912107. Accessed October 11, 2017.

297. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatr*. 2002;2:1. doi:10.1186/1471-2318-2-1.

298. O'Donovan A, Pantell MS, Puterman E, Dhabhar FS, Blackburn EH, Yaffe K, Cawthon RM, Opresko PL, Hsueh W-C, Satterfield S, Newman AB, Ayonayon HN, Rubin SM, Harris TB, Epel ES, Health Aging and Body Composition Study for the HA and BC. Cumulative inflammatory load is associated with short leukocyte telomere length in the Health, Aging and Body Composition Study. *PLoS One*. 2011;6(5):e19687. doi:10.1371/journal.pone.0019687.

299. Demissie S, Levy D, Benjamin EJ, Cupples LA, Gardner JP, Herbert A, Kimura M, Larson MG, Meigs JB, Keaney JF, Aviv A. Insulin resistance, oxidative stress, hypertension, and leukocyte telomere length in men from the Framingham Heart Study. *Aging Cell*. 2006;5(4):325-330. doi:10.1111/j.1474-9726.2006.00224.x.

300. Seo AY, Leeuwenburgh C. The Role of Genome Instability in Frailty: Mitochondria versus Nucleus. *Nestle Nutr Inst Workshop Ser*. 2015;83:19-27. doi:10.1159/000382055.

301. Wu I-C, Shiesh S-C, Kuo P-H, Lin X-Z. High oxidative stress is correlated with frailty in elderly chinese. *J Am Geriatr Soc*. 2009;57(9):1666-1671. doi:10.1111/j.1532-5415.2009.02392.x.

302. Syddall H, Roberts HC, Evandrou M, Cooper C, Bergman H, Sayer AA. Prevalence and correlates of frailty among community-dwelling older men and women: findings from the Hertfordshire Cohort Study. *Age Ageing*. 2010;39(2):197-203. doi:10.1093/ageing/afp204.

303. Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. *Age Ageing*. 2015;44(1):162-165. doi:10.1093/ageing/afu148.

304. Kelaiditi E, Cesari M, Canevelli M, Abellan van Kan G, Ousset P-J, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salva A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten JL, Vellas B. Cognitive frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. *J Nutr Health Aging*. 2013;17(9):726-734. doi:10.1007/s12603-013-0367-2.

ORIGINAL PUBLICATIONS

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

SBN 978-951-51-5149-0 (paperback)

ISBN 978-951-51-5150-6 (PDF)

Hansaprint, Helsinki 2019